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Health Assessment Document for Tetrachloroethylene (Perchloroethylene)

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Review Draft

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16. ABSTRACT

Tetrachloroethylene (PCE) is a volatile solvent with important commercial applications. It has been detected in the ambient air of a variety of urban and nonurban areas of the United States. It has less frequently been detected in water but has been monitored generally at levels of 1 ppb or less. The lowest-observed-adverse-effect-level, based on central nervous system dysfunction, is about 100 ppm (678 mg/m^3). Toxicity testing in experimental animals, coupled with limited human data, suggests that long-term exposure of humans to ambient levels of PCE is not likely to represent a health concern. At the current time, the teratogenic potential of PCE for humans is unknown; the mammalian animal tests performed to date do not indicate any significant teratogenic potential. Although PCE epoxide has been found to be positive with respect to mutagenicity in bacterial systems, the data on pure PCE suggest that if it is mutagenic, it is a weak mutagen. PCE has been demonstrated to induce malignant tumors of the liver in mice. This constitutes limited evidence that PCE may be carcinogenic in humans. Because existing epidemiologic data for PCE is inconclusive, the overall ranking according to the criteria of the International Agency for Research on Cancer (IARC) would suggest that PCE is possibly carcinogenic in humans.

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U.S. ENVIRONMENTAL PROTECTION AGENCY
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This report is an external draft for review purposes only and does not constitute Agency policy. Mention of trade names or commercial products does not constitute endorsement or recommendation for use.

PREFACE

The Office of Health and Environmental Assessment has prepared this health assessment to serve as a "source document" for EPA use. Originally the health assessment was developed for use by the Office of Air Quality Planning and Standards to support decision-making regarding possible regulation of PCE as a hazardous air pollutant. However, at the request of the Agency's Work Group on Solvents the assessment scope was expanded to address multimedia aspects.

In the development of the assessment document, the scientific literature has been inventoried, key studies have been evaluated, and summary/conclusions have been prepared so that the chemical's toxicity and related characteristics are qualitatively identified. Observed-effect levels and dose-response relationships are discussed, where appropriate, so that the nature of the adverse health responses is placed in perspective with observed environmental levels.

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1. EXECUTIVE SUMMARY

Tetrachloroethylene (PCE) is a moderately volatile chlorinated hydrocarbon which has important commercial applications in the dry cleaning of fabrics and in the degreasing of fabricated metal parts. It is estimated that approximately 300,000 metric tons were produced in the United States in 1980. Approximately 90 percent of production is estimated to be released eventually to the atmosphere. Because PCE is relatively insoluble in water (150 mg/l) and has a vapor pressure of 0.19 pascals at 20°C, PCE in natural waters would be conveyed to the atmosphere rapidly, through evaporation. There are no known or expected natural sources of emissions.

PCE has been detected in the ambient (natural environment) air of a variety of urban and nonurban areas of the United States and other regions of the world. Levels can range from trace amounts in rural areas to as much as 10 parts per billion (ppb) or 0.068 mg/m^3 in some large urban centers. The global average background level is estimated at about 25 parts per trillion (ppt) or 0.175×10^{-3} mg/m^3. It is detected less frequently in water, because it is not appreciably soluble; but PCE has been monitored in some surface and drinking waters, generally at levels of 1 ppb or less. In certain instances involving contamination of groundwater, much higher levels have been reported. Although there is very limited information on the behavior of PCE in soil, PCE can be expected to leach through soils of low (< 0.1 percent) organic carbon content. The amount of PCE adsorbed to soils is dependent on the partition coefficient, the organic carbon content, and the concentration of PCE in the liquid phase.

In the troposphere, a region of the atmosphere extending to between 8 and 16 kilometers above the earth's surface, PCE undergoes photochemical degradation to the extent that its estimated lifetime is appreciably less than 1 year. Little PCE is expected to be conveyed to the stratosphere. Recent studies have shown that, in real atmospheres, neither atomic chlorine- nor hydroxy radical-induced photooxidation of PCE generates substantial concentrations of ozone or other oxidants; thus, PCE is not believed to be a significant factor in production of photochemically-induced pollution often experienced near large urban centers. Because of the reduced solar flux in winter and seasonal variations in hydroxy radical concentration, PCE levels in ambient air are expected to be higher in winter than in summer. On a daily basis, PCE levels fluctuate considerably.

Inhalation is the principal route by which PCE enters the body. Ingestion of drinking water contaminated by PCE is a secondary source of exposure. During inhalation, PCE is absorbed by the blood and distributed throughout the body. Controlled studies with human volunteers (at 100 ppm) have shown that pulmonary steady-state conditions are reached between 3 and 4 hours. Physical activity increases uptake. At levels approaching those found or expected in ambient air, the time required to reach steady-state conditions may be considerably longer. Once body equilibrium or steady-state has been reached, no further uptake is possible. There is evidence that PCE will partition selectively into lipid-rich tissues with chronic or long-term exposure to even low ambient air concentrations until steady-state is attained. Because of its lipophilic nature, PCE is expected to cross membrane barriers in the body. Most inhaled PCE is excreted via the lungs in unchanged form. Both controlled and occupational exposures of humans indicate that the principal urinary excretion product of PCE metabolism is trichloroacetic acid. Controlled studies with humans have demonstrated that PCE metabolism (urinary trichloroacetic acid) represents 2 percent or less of the amount of PCE absorbed. Studies in rats and mice suggest that metabolism of PCE is a saturable process. In humans, saturation would not be expected until exposure levels approximate 100 ppm (678 mg/m^3).

Toxicity testing in experimental animals, coupled with limited human data derived principally from overexposure situations, suggests that long-term exposure of humans to environmental levels of PCE is not likely to present a serious health concern.

Decrements in task performance and coordination are the first gross signs of central nervous system (CNS) depression and behavioral alterations observed in controlled human studies in which individuals were exposed to about 100 ppm (678 mg/m^3) for up to 7 hours. More sensitive tests, however, would have to be performed to determine if PCE affects the nervous system at even lower concentrations.

Evidence in rodent species suggests that PCE has the potential to cause liver damage with acute or prolonged exposure at levels that, in humans, would cause only slight CNS depression. However, there are insufficient data to estimate the lowest levels of PCE that are associated with adverse effects upon the liver in humans.

The lowest observed-adverse-effect level (LOAEL), based on CNS dysfunction, is about 100 ppm (678 mg/m^3). However, the LOAEL may not be sufficiently protective of human health when one considers that intermittent or prolonged exposure of animals to PCE has been observed to result in liver and kidney damage at levels exceeding 200 ppm (1,356 mg/m^3). It should be noted that liver damage in humans is generally associated with short-term exposures greatly in excess of 100 ppm (678 mg/m^3). The LOAEL is defined as the lowest exposure level in a study or group of studies which produces statistically significant increases in frequency or severity of adverse effects between the exposed population and its appropriate control.

The mammalian animal tests performed to date do not indicate any significant teratogenic potential of PCE in the species tested. On this basis, there is no evidence to suggest that the conceptus is uniquely susceptible to the effects of PCE. The anatomical effects observed reflect delayed development and can be considered reversible. It is important to note, however, that the reversible nature of an embryonic/fetal effect in one species might, in another species, be manifested in a more serious and irreversible manner. At the current time, the teratogenic potential of PCE for humans must be considered unknown.

Tetrachloroethylene has been evaluated for its ability to cause gene mutation, chromosomal aberrations, unscheduled DNA synthesis, and mitotic recombination. These tests were conducted using bacteria, Drosophila, yeast, cultured mammalian cells, whole mammal systems, and cytogenetic analyses of exposed humans. Certain technical and commercial samples of PCE elicited increased responses in the Ames bacterial test, a yeast mitotic recombination assay, a host-mediated assay using Salmonella, and DNA repair tests. Exogenous metabolic activation was not required for detection of these increased effects. In general, the responses were weak and observed at high concentrations that were cytotoxic; dose-dependent relationships were not established. The positive findings may be the result of mutagenic contaminants and/or added stabilizers. There have been several other tests of commercial and technical samples of PCE which have been reported as negative. The epoxide of PCE, which is thought to be the active biological intermediate, was found to be positive in bacterial studies.

Tetrachloroethylene has been demonstrated to induce malignant tumors of the liver in both male and female mice of the B6C3F1 strain. This constitutes limited evidence that PCE may be carcinogenic in humans. It should be recognized that a substantial part of the scientific community believes that the mouse liver overreacts to chlorinated organic compounds, in contrast to that of the rat, and that the induction of liver cancer in the mouse represents only a promoting action for spontaneous liver tumors which normally occur with substantial incidence.

According to the criteria of the International Agency for Research on Cancer (IARC), the data supporting the carcinogenicity of PCE must be classified as "limited." Because existing human epidemiological data for PCE is inconclusive, its overall IARC ranking should be Group 3, meaning that there is inadequate evidence for classifying PCE as a human carcinogen.

2. INTRODUCTION

Tetrachloroethylene (PCE) is one member of a family of unsaturated chlorinated aliphatic compounds. Other common names/acronyms are perchloroethylene, Perk, PER, and PERC. Its synonyms include carbon dichloride, tetrachloroethene, and 1,1,2,2-tetrachloroethylene.

Tetrachloroethylene, though a water and solid waste contaminant, is primarily of interest in ambient air exposure situations. It is released into ambient air as a result of evaporative losses during production, storage, and/or use. It is not known to be generated from natural sources. It has negligible photochemical reactivity in the troposphere and is removed by scavenging mechanisms, principally via hydroxyl radicals.

The scientific data base is limited with reference to the effects of PCE on humans. Effects on humans have generally been ascertained from studies involving individuals occupationally or accidentally exposed. During such exposures, the concentrations associated with adverse effects on human health were either unknown or far in excess of concentrations found or expected in ambient air. Controlled PCE exposure studies have been directed toward elucidating the effects on the central nervous system, effects on clinical chemistries, and pharmacokinetic parameters of PCE exposure.

Since epidemiological studies have not been able to assess adequately the overall impact of PCE on human health, it has been necessary to rely greatly on animal studies to derive indications of potential harmful effects. Although animal data cannot always be extrapolated to humans, indications of probable or likely effects among animal species increase confidence that similar effects may occur in humans.

This document is intended to provide an evaluation of the scientific data base concerning PCE. It is believed that the literature has been comprehensively reviewed and critically evaluated through September 1983. The publications cited in this document represent a majority of the known scientific references to PCE. Reports which had little or no bearing upon the issues discussed were not cited.

3. GENERAL BACKGROUND INFORMATION

3.1 PHYSICAL AND CHEMICAL PROPERTIES

Tetrachloroethylene, also called PCE (1,1,2,2-tetrachloroethylene or perchloroethylene), is a colorless, heavy liquid with a chloroform-like odor. It is used as a solvent for organic substances and is commercially important as a solvent in the dry cleaning of fabrics and in the degreasing of metals. It has a molecular weight of 165.85 and is relatively insoluble in water (150 mg/l) (Handbook of Chemistry and Physics, 1976; Chemical and Process Technology Encyclopedia, 1974). Its CAS registry number is 127184. In air, at standard temperature and pressure, 1 part per million (ppm) is equivalent to 6.78 mg/m^3.

Tetrachloroethylene has negligible photochemical reactivity (Dimitriades et al., 1983) and, in the troposphere, is decomposed via free radical mechanisms. When in contact with water for prolonged periods, PCE slowly decomposes to yield trichloroacetic and hydrochloric acids. Upon prolonged storage in light, it was reported to decompose slowly to trichloroacetyl chloride and phosgene by autooxidation (Hardie, 1966). At 700°C, it decomposes, when in contact with activated charcoal, to hexachloroethane and hexachlorobenzene (Gonikberg, 1956). Tetrachloroethylene has a boiling point of 121.1°C at 760 mm Hg and a vapor pressure of 14 torr at 20°C. MacKay et al. (1982) have calculated a vapor pressure of 19 torr at 25°C.

The chemical reactivity of PCE has been discussed by Bonse and Henschler (1976) in terms of the electron-inductive effect of the chlorine atoms, which reduce electron density about the ethylene bond. This effect, in combination with a steric protective effect afforded by the chlorine atoms, provides increased stability against electrophilic attack. This is exemplified in the reaction of PCE with ozone. Compared to ethylene and less-substituted chlorination hydrocarbons, PCE has a low rate of reaction (Williamson and Cvetanovik, 1968).

3.2 PRODUCTION

Tetrachloroethylene may be produced by several processes:

1. Chlorination of trichloroethylene:

$$CHCl = CCl_2 + Cl_2 \xrightarrow[SbCl_3]{80^\circ C} CHCl_2\ CCl_3$$

$$2CHCl_2CCl_3 + Ca(OH)_2 \xrightarrow{80^\circ C} Cl_2C = CCl_2 + CaCl_2 + 2H_2O$$

2. Dehydrochlorination of S-tetrachloroethane:

$$CHCl_2\text{-}CHCl_2 + Cl_2 \longrightarrow CCl_2 = CCl_2 + 2HCl$$

3. Oxygenation of S-tetrachloroethane:

$$2CHCl_2CHCl_2 + O_2 \longrightarrow 2CCl_2 = CCl_2 + 2H_2O$$

4. Chlorination of acetylene:

$$CCl_2 = CCl_2 + Cl_2 \xrightarrow{200^\circ C} CCl_3\text{-}CCl_3$$

$$CH \equiv CH + 3\ CCl_3CCl_3 \xrightarrow[\text{catalyst}]{200\text{-}400^\circ C} 4CCl_2 = CCl_2 + 2HCl$$

5. Chlorination of hydrocarbons:

$$\underset{\text{(propane)}}{C_3H_8} + 8\ Cl_2 \longrightarrow CCl_2 = CCl_2 + CCl_4 + 8HCl$$

$$2CCl_4 \longrightarrow CCl_2 = CCl_2 + 2Cl_2$$

6. Oxychlorination of 1,2-dichloroethane:

$$2C_2H_4Cl_2 + 5Cl_2 \longrightarrow C_2H_2Cl_4 + C_2HCl_5 + 5HCl$$

$$C_2H_2Cl_4 + C_2HCl_5 \longrightarrow C_2HCl_3 + 2HCl + CCl_2 = CCl_2$$

$$7HCl + 1.75\ O_2 \longrightarrow 3.5\ H_2O + 3.5\ Cl_2$$

$$2C_2H_4Cl_2 + 1.5\ Cl_2 + 1.75\ O_2 \longrightarrow C_2HCl_3 + CCl_2 = CCl_2 + 3.5\ H_2O$$

The majority of PCE producted in the United States is derived from the oxychlorination of 1,2-dichloroethane or via chlorination of hydrocarbons (Lowenheim and Moran, 1975).

In 1980, 347,859 metric tons of PCE were produced (U.S. International Trade Commission, 1980). The major producers and production capacities are shown in Table 3-1. Locations of U.S. production facilities are shown in Figure 3-1.

Imports of PCE may be sizeable, although they are partially offset by exports. Most of the PCE imported is produced in Belgium, Italy, France, and Canada (Chemical Marketing Reporter, 1979a).

TABLE 3-1. MAJOR U.S. PRODUCERS OF PCE[a]

Organization	Yearly capacity, MT[a]
Dow Chemical	320
PPG	200
Vulcan	200
Diamond Shamrock	165
Ethyl Corporation[b]	
E. I. du Pont de Nemours[c]	160

[a] Adapted from Chemical Economics Handbook (SRI, 1982). MT = Metric tons.

[b] Recently announced withdrawal from production (Halogenated Solvents Industry Alliance, 1983)

[c] Output for captive use only.

3.3 USE

Tetrachloroethylene has the following uses (Gosselin et al., 1976; Fishbein, 1977): (1) dry cleaning solvent; (2) textile scouring solvent; (3) dried vegetable fumigant; (4) rug and upholstery cleaner; (5) stain, spot, lipstick, and rust remover; (6) paint remover; (7) printing ink ingredient; (8) heat transfer media ingredient; (9) chemical intermediate in the production of other organic compounds; and (10) metal degreaser.

Testimony provided by the International Trade Commission to the Secretary of the Treasury in March 1979 stated that dry cleaning consumes approximately 75 percent of U.S. PCE production and imports (Chemical Marketing Reporter, 1979a). About 72 percent of commercial dry cleaning plants are estimated to use PCE (U.S. EPA, 1979).

3.4 EMISSIONS

Emissions of PCE arise during its production, from its use as a chemical intermediate in industrial processes, from storage containers, during disposal, and from its use as a solvent. Because emissions are almost exclusively to the atmosphere, the information presented in this section focuses on air. Few data are available concerning discharges to water. The section dealing

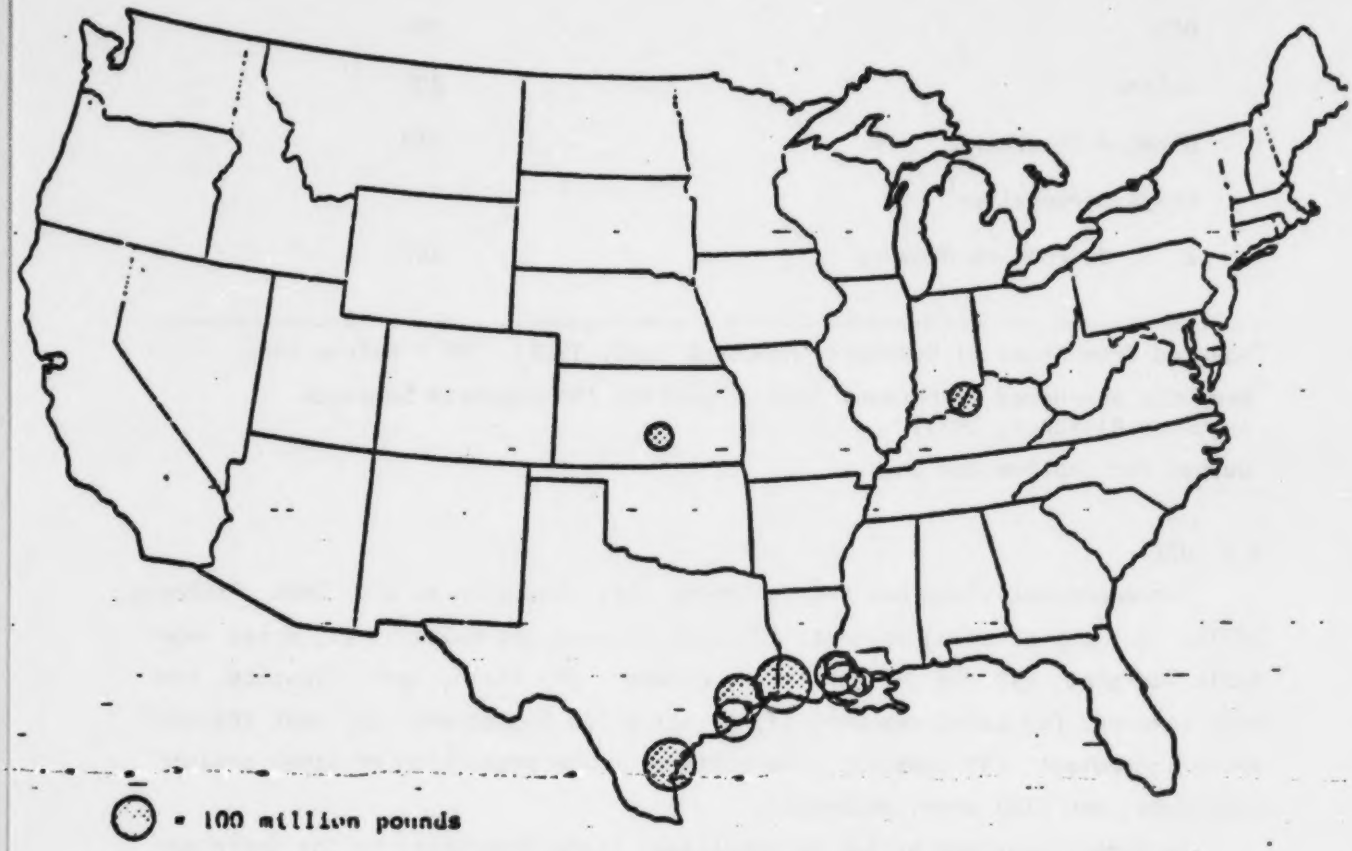
= 100 million pounds

Figure 3-1. Locations of U.S. PCE production facilities producing more than 100 million pounds.

Source: Fuller, 1976.

with monitoring indicates that discharges to water probably occur. Emissions estimates reflect a diversity of sources throughout the country. Dry cleaning operations are located primarily in urban areas. Approximately 26,000 establishments are estimated to exist, according to Bureau of Census data (U.S. EPA, 1979).

In 1977, global emissions were estimated at 570,000 ± 285,000 metric tons (Singh et al., 1979). It was also estimated that emissions accounted for approximately 90 percent of the amount of PCE produced (300,000 metric tons) in the United States.

3.5 ENVIRONMENTAL FATE AND TRANSPORT

The potential for ambient air and water mixing ratios of PCE to pose a hazard to human health is influenced by many processes. Such factors include transformation into secondary pollutants of concern and degradation rates in air and water.

3.5.1 Ambient Air

3.5.1.1 Tropospheric Reactivity--Reaction with the hydroxyl radical ($\cdot$OH) is the principal process by which many organic compounds, including PCE, are scavenged from the troposphere. Hydroxyl radicals are produced when O_3 is irradiated, resulting in excited atomic oxygen, which then reacts with water vapor. The tropospheric lifetime of a compound is related to the $\cdot$OH mixing ratio according to the expression:

$$\tau_{\text{lifetime}} = \frac{1}{k\,[\text{OH}]} \qquad (3\text{-}1)$$

where k is the rate constant of reaction.

Singh et al. (1979, 1981) calculated a tropospheric residence of PCE of about 68 days. This calculation was based on an average 24-hour $\cdot$OH abundance of 10^6 molecules cm^{-3} in the boundary layer of a polluted atmosphere. Justification for this $\cdot$OH mixing ratio stems from the field studies of Calvert (1976) and from Singh and coworkers (1979a). Because this $\cdot$OH mixing ratio is more typical of summer months, Singh et al. (1981) suggested that a seasonally adjusted mixing ratio would result in a longer chemical residence time. If a seasonally-averaged $\cdot$OH mixing ratio of 4×10^5 molecules cm^{-3} (a level supported by the field measurements of Campbell et al., 1979) and a weighted global average temperature (265°K), an average residence time of PCE would be calculated to be 292 days or 0.8 years (Singh et al., 1979).

Estimations of a residence time of PCE of one year or less have been reported by a number of investigators (Altshuller, 1980; Singh et al., 1978a; Singh, 1977; Crutzen et al., 1978; Lillian et al., 1975; Yung et al., 1975; Pearson and McConnell, 1975).

Dimitriades et al. (1983) calculated a very low tropospheric reactivity for PCE based on observations that ambient levels of PCE are constant. Atmospheric consumption of PCE is 0.02 percent per daylight hour.

Higher levels of ·OH have been reported for the southern hemisphere compared to those in the northern hemisphere (Singh, 1978). This gradient probably is due to the fact that carbon monoxide levels are much higher in the northern hemisphere, thus reducing ·OH levels (Singh, 1978). Measurements of PCE and other reactive halocarbons indicate that mixing ratios are higher in the northern hemisphere where the ·OH mixing ratio is low and where most of the PCE is released (Singh et al., 1978b).

Chamber studies indicate that PCE, on irradiation in the presence of other atmospheric constituents, can be transformed into secondary products. This area of study has been recently reviewed and further explored by Dimitriades et al. (1983). These investigators have confirmed that PCE, under smog chamber conditions, reacts to form O_3 and ozone precursors by means of a Cl-initiated photooxidation mechanism. However, such photooxidation is not expected to occur in the real atmosphere at a rate high enough for substantial O_3 production. It is the authors' contention that Cl atoms are effectively scavenged by the hydrocarbons normally present in the atmosphere; thus, PCE was judged to contribute less to O_3 production than equal concentrations of ethane. Ethane is regarded by the authors to be a boundary species separating the reactive volatile organics from the unreactive ones.

Studies on PCE reactions with O_3, O, and ·OH have indicated that rate constants are lower than with Cl (Dimitriades et al., 1983).

Gay et al. (1976) had determined that trichloroacetyl chloride was a photooxidation product of PCE in smog chamber studies. Dimitriades et al. (1983) found that, on irradiation, the only product observed was CO. Phosgene was not detected. When 2 ppm (13.6 mg/m^3) PCE and 20 ppb trichloroacetyl chloride were irradiated together, the phosgene level reached 0.1 ppm.

Phosgene production from the photochemical oxidation of PCE in the presence of other substances has been reported by others (Lillian et al., 1975; Gay et al., 1976). The extent to which phosgene may be formed in real atmospheres, based on smog chamber results, would also be expected to be minimal.

3.5.1.2 Tropospheric Removal Mechanisms for PCE--The reaction sequence by which PCE may be scavenged from the troposphere is as follows (Graedel, 1978):

$$C_2Cl_4 + HO\cdot \longrightarrow HOC(Cl)_2C(Cl)_2\cdot$$

$$HOC(Cl)_2C(Cl)_2\cdot + O_2 \longrightarrow HOC(Cl)_2C(Cl)_2O_2\cdot$$

$$HOC(Cl)_2C(Cl)_2O_2\cdot \xrightarrow[\text{abstraction}]{\text{oxygen}} HOC(Cl)_2C(Cl)_2O\cdot$$

$$HOC(Cl)_2C(Cl)_2O\cdot \longrightarrow HOC(Cl)_2\cdot + COCl_2$$

$$HOC(Cl)_2\cdot + O_2 \longrightarrow COCl_2 + HO_2\cdot$$

Howard (1976) suggested that the reaction path for the atmospheric oxidation of PCE may follow the scheme below, leading to the production of oxalyl chloride:

$$C_2Cl_4 + \cdot OH \longrightarrow C_2Cl_2OH\cdot$$

$$\longrightarrow CCl_2CClOH\cdot + Cl\cdot \tag{3-3}$$

$$CCl_2CCl_2OH\cdot + O_2 \longrightarrow O_2CCl_2CCl_2OH$$

$$O_2CCl_2CCl_2OH + NO \longrightarrow COClCCl_2OH\cdot + NO_2 + Cl\cdot$$

$$\cdot OH + COClCCl_2OH \longrightarrow COClCOCl + H_2O + Cl\cdot$$

Compared to other ethylene compounds studies, Howard (1976) reported that PCE exhibits unusually low reactivity toward hydroxyl radicals.

Snelson et al. (1978) suggested that trichloroacetyl chloride and phosgene would hydrolyze to the corresponding chloroacetic acids and hydrogen chloride via homogeneous gas phase hydrolysis. The acids then would presumably be washed out of the atmosphere.

The environmental significance of the production of phosgene from PCE has been discussed by Singh and coworkers (Singh et al., 1975; Singh, 1976). As PCE emissions are likely to be higher in urban areas, the reactivity of this halocarbon may result in concentrations of phosgene in the low ppb range during adverse meteorological conditions in and around urban centers (Singh, 1976). It should be noted that overt adverse health damage would not be expected at these phosgene levels. Considering the smog chamber results of Dimitriades et al. (1983), in which PCE was found to have negligible reactivity, it appears unlikely that phosgene would be produced at other than trace levels. The results of Singh and coworkers indicate that negligible tropospheric loss via gas phase hydrolysis would be expected, because phosgene is very stable in the gas phase. The two important sinks cited were heterogeneous decomposition and slow liquid phase hydrolysis. Singh (1976) concluded that phosgene is removed slowly from the atmosphere. Rainfall appears to lower atmospheric levels of phosgene (Singh et al., 1977a). On the other hand, phosgene has been reported to hydrolyze to CO_2 and HCl rapidly in liquid water. Manogue (1958) reported a half-life of 0.1 second at 25°C. Thus, it is not expected to persist in the troposphere because of rainout and hydrolysis in aqueous aerosols.

The observed diurnal variations in PCE levels suggest that PCE has higher mixing ratios in the morning and evening hours than at other times (Lillian et al., 1975; Singh et al., 1977a). Ohta et al. (1977) reported that mixing ratios tended to be highest on cloudy days and lowest on rainy days.

Solar flux is a major factor in the rate at which PCE is removed from the atmosphere. Singh et al. (1977a) suggested that the reduced solar flux in winter months would permit a much longer transport of PCE because of reduced reactivity. The effect of solar flux was calculated by Altshuller (1980) who estimated that a 1 percent consumption of PCE by reaction with ·OH would take 14 days during the month of January as opposed to one day in July.

While the studies of Gay et al. (1976) indicate that trichloroacetyl chloride may be formed through chlorine atom migration in an epoxide intermediate, evaluation of ·OH and oxygen atom rate constants indicate that less than 1 percent of PCE in ambient air reacts with atomic oxygen and, of the activated epoxides formed, only a small percentage undergo rearrangement (Graedel, 1978).

3.5.2 Water

Jensen and Rosenberg (1975) investigated the degradability of PCE (≃ 0.1 to 1.0 ppm) in both open and closed systems, with sea water and fresh water. In open aquaria, with 20 l of sea water, PCE levels decreased 50 percent within 200 hours (daylight). In a closed system, levels decreased approximately 25 percent over the same interval (daylight). It was reported that PCE levels in boiled, deionized water in a closed system did not exhibit any significant decrease after 8 days. Analysis was by headspace collection, followed by gas chromatography-electron capture detection (GC-ECD) quantification. Accuracy and limits of detection were not reported. Variation in detector sensitivity was checked daily by an injection of PCE in hexane.

Dilling et al. (1975) reported that PCE in water slowly decomposes to form trichloroacetic and hydrochloric acids. The evaporation rate was determined by dissolving 1 ppm (w/w) PCE in 200 ml of water. Solution temperature was approximately 25°C. The solution was stirred magnetically in a sealed system. Quantification was made by mass spectroscopy. The evaporation rate of PCE, determined from measurements over a 2-week period, was characterized by a 50 percent decrease in the initial mixing ratio in 24 to 28 minutes. The stirring speed had a marked effect on the evaporation rate. With no stirring except for 15 seconds every 5 minutes, the time required for 50 percent depletion ranged from 72 to 90 minutes. The evaporative half-life was 27 ± 3 minutes. Addition of dry, granular bentonite clay (500 ppm) appeared to increase the rate of disappearance by 33 percent at 20 minutes. However, when the clay was allowed to remain in contact with purified water for several days and then added to the solution, there was no change in the rate compared with control. In closed system investigations, Dilling et al. (1975) used dry, powdered dolomitic limestone, bentonite, and peat moss to determine the adsorption rate for PCE. With 500 ppm bentonite, there was a 22 percent absorption after 30 minutes. There was no further absorption. Addition of limestone resulted in a 50 percent depletion in 20 ± 2 minutes. Addition of silica sand had no effect on the disappearance rate. When 500 ppm peat moss was added, up to 0.4 ppm PCE was absorbed after 10 minutes. At longer times, no further absorption was observed. It was concluded that evaporation probably is the major pathway by which PCE is lost from water.

In reactivity studies, Dilling et al. (1975) found that sunlight had the greatest effect on the rate of PCE disappearance. The PCE level in water was

6 μM. Over a 12-month period, in which PCE solutions were stored in the dark as well as in the light, PCE levels decreased from 1 ppm (0 time), to 0.63 ppm (6 months), to 0.35 ppm (12 months) in samples stored in the dark. In the light-exposed solution, the level decreased to 0.52 ppm (6 months), and 0.24 ppm (12 months).

Schwarzenbach et al. (1979), in measurements of PCE levels in Lake Zurich, reported findings compatible with those of Dilling et al. (1975) in that evaporation is the dominant elimination process from surface waters. The annual release to the atmosphere was estimated by applying a steady-state mass balance model. Based on vertical concentration profiles from the lake, about 240 kg PCE was released from the central basin annually.

3.6 LEVELS OF EXPOSURE

3.6.1. Mixing Ratios

3.6.1.1 Ambient Air--A wide variety of halogenated aliphatic hydrocarbons, including PCE, have been detected in ambient air. Ambient measurements of PCE have been conducted in both the United States and other areas of the world. These determinations provide a basis for assessing the levels to which human populations may be exposed.

Measured ambient air concentrations differ widely and undoubtedly reflect the influences of a variety of factors, e.g., meteorological conditions, tropospheric reactivity, diurnal variations, sampling times, and source emissions.

Table 3-2 provides summary information regarding background and urban concentrations of PCE. It should be noted that, in general, these values reflect short sampling times.

Measurements of ground-level samples by Singh et al. (1978b), in both the northern and southern hemispheres, gave average background levels of 0.040 ± 0.012 ppb ($2.7 \times 10^{-4} \pm 0.08 \times 10^{-4}$ mg/m^3) and 0.012 ± 0.003 ppb (0.081×10^{-3} $\pm 0.02 \times 10^{-3}$ mg/m^3), respectively. Globally, the average background level of PCE was 0.026 ± 0.007.7 ppb ($1.7 \times 10^{-4} \pm 0.47 \times 10^{-4}$ mg/m^3); the coefficient of variation was 27 percent. The average urban level of PCE was found to be about 30 times the background level.

Evidence for considerable variability in ambient air levels of PCE was shown by Lillian et al. (1975). The authors attributed the variability of PCE to its tropospheric reactivity (reaction with hydroxyl radicals).

TABLE 3-2. AMBIENT AIR MIXING RATIOS OF PCE MEASURED AT SITES AROUND THE WORLD

Location	Date of Measurement	Reported Concentration, ppm (mg/m^3)			Reference
		Maxium	Minimum	Average	
Alabama[a]					
Birmingham	April 12-22, 1977	0.008	0	0.001 ± 0.003	Pellizzari, 1979
Arizona					
Grand Canyon[a]	Nov. 28-Dec. 5, 1977	0	0	0	Pellizzari, 1979
Phoenix	Apr. 23-May 6, 1979[b]	3.696 (0.025)	0.129	0.9938 ± 0.7155 (0.0008)	Singh et al., 1981 (0.0067 ± 0.0048)
California					
San Bernardino Mtns.	Fall, 1972	0.09 (6.1×10^{-4})			Simmonds et al., 1974
Badger Pass	May 12-16, 1976	0.03 (2×10^{-4})			Singh et al., 1977a
Point Arena	1976	0.03 (2×10^{-4})			Singh et al., 1978a
Stanford Hills	Nov. 24-30, 1975	0.04 (2.6×10^{-4})			Singh et al., 1977b
Point Reyes	Dec. 2-12, 1975	0.043 (2.9×10^{-4})			Singh et al., 1977b
Dominguez	May 14, 1976			2.9	Pellizzari, 1977
El Cajon	April 9, 1975			0.31	Su and Goldberg, 1976
La Jolla	Apr 9, 1974-Jan 6, 1976	2.3	0	0.53 ± 0.63	Su and Goldberg, 1976
Los Angeles	Sept. 22, 1972- April 19, 1979	2.2	0.067	1.1 ± 0.45	Simmonds et al., 1974; Singh, 1976; Singh et al., 1977a; Su and Goldberg, 1976
Menlo Park	Nov. 24-30, 1975			0.20 ± 0.21	Singh et al., 1977a
Mill Valley	Jan. 1-27, 1977			0.065 ± 0.075	Singh et al., 1979
Mt. Cuyamaca	Mar. 15, 1975			0.22	Su and Goldberg, 1976

TABLE 3-2. (continued)

Location	Date of Measurement	Reported Concentration, ppm (mg/m^3) Maxium	Minimum	Average	Reference
California					
Oakland	June 30-July 8, 1979	0.64	0.12	0.31 ± 0.17	Singh et al., 1979; Singh et al., 1981
Palm Springs	May 5-11, 1976	1.1	0.12	0.28 ± 0.084	Singh et al., 1978a
Riverside	April 25, 1977-July 12, 1980	0.98	0.37	0.49 ± 0.13	Singh et al., 1979; 1980
San Jose	Aug. 21-27, 1978			1.1 ± 0.036	Singh et al., 1979
Santa Monica	April 6, 1974			2.3	Su and Goldberg, 1976
Upland	Aug. 13-Sept. 23, 1977	1.1	0.01	0.19 ± 0.35	Pellizzari, 1979
Colorado[a]					
Denver	Jun 16-26, 1980	0.47	0.24	0.39 ± 0.077	Singh et al., 1980
Delaware					
Delaware City	July 8-10, 1974	0.51 (0.0034)	<0.02 (<0.0001)	0.24 (0.0016)	Lillian et al., 1975
Louisiana					
Baton Rouge, Geismar, and Plaquemine	Fall, 1978	0.18 (0.001)	.001 (0.007 x 10^{-3})	0.017 (0.118 x 10^{-3})	Pellizzari et al., 1979b
Maryland					
Baltimore	July 11-12, 1974	0.29 (0.0019)	<0.02 (<0.0001)	0.18 (0.0012)	Lillian et al., 1975
Michigan					
Detroit	Oct 27-Nov 5, 1978[b]	2.16 (0.004)	<0.1 (<0.001)	0.35 (0.002)	Evans et al., 1979
New Jersey					
Bayonne	March, 1973-Dec., 1973	8.2 (0.0055)	0.30 (0.0020)	1.63 (0.0110)	Lillian et al., 1975

TABLE 3-2. (continued)

Location	Date of Measurement	Reported Concentration, ppm (mg/m^3)		Average	Reference
		Maximum	Minimum		
New Jersey					
New Brunswick	-	-	0.5 (0.003)	-	Lillian et al., 1976
New Brunswick	-	-	0.12 (0.0081)	-	Lillian and Singh, 1974
Seagirt	June 18-19, 1974	0.88 (0.059)	0.10 (0.067)	0.32 (0.0022)	Lillian et al., 1975
Sandy Hook	July 2, 1974	1.4 (95×10^{-4})	0.15 (10×10^{-4})		Lillian et al., 1975
Boundbrook, Rahway, Edison and Passaic	Sept 18-22, 1978	58 (0.394)[c]	trace	30.9 (0.210)	Pellizari et al., 1979
Batsto[a]	Feb. 26-Dec. 29, 1979	0.53	0	0.034	Bozzelli et al., 1980
Bridgeport[a]	Sept. 22, 1977	0.041	0	0.020	Pellizzari and Bunch, 1979
Burlington[a]	Sept. 19, 1977			0.027	Pellizzari and Bunch, 1979
Camden[a]	April 3-Oct. 24, 1979	30	0	1.8 ± 6.2	Bozzelli et al., 1980
Carlstadt[a]	Sept. 28-30, 1978	5.5	1.1	3.5 ± 2.3	Pellizzari et al., 1979
Edison[a]	March 24, 1976- Sept. 24, 1978	8.7	0.11	2.8 ± 3.1	Pellizzari et al., 1979; Pellizzari, 1978; Bunn et al., 1975
Elizabeth[a]	Sept. 15, 1978- Dec. 29, 1979	14	0	2.0 ± 3.1	Bozzelli et al., 1980; Pellizzari, 1979
Fords[a]	Mar. 26, 1976- Sept. 27, 1978	5.6	0	2.8 ± 2.7	Pellizzari et al., 1979; Pellizzari, 1977
Middlesex[a]	July 23-28, 1978	0.21	0	0.068 ± 0.090	Bozzelli and Kebbekus, 1979
Newark[a]	Mar. 23, 1976- Dec. 29, 1979	32	0	1.3 ± 3.1	Bozzelli and Kebbekus, 1979; Bozzelli et al., 1980; Pellizzari, 1977

TABLE 3-2. (continued)

Location	Date of Measurement	Reported Concentration, ppm (mg/m^3) Maxium	Minimum	Average	Reference
New Jersey					
Rahway[a]	Sept. 20-22, 1978	5.0	2.7	3.8 ± 1.2	Bozzelli and Kebbekus, 1979; Bozzelli et al., 1980
Rutherford[a]	May 1, 1978-Dec 29, 1979	9.2	0	0.89 ± 0.14	Bozzelli et al., 1980
Somerset[a]	July 18-26, 1978	0.068	0	0.036 ± 0.26	Bozzelli and Kebbekus, 1979
South Amboy	Jan. 27-Dec. 29, 1979	2.2	0	0.21 ± 0.53	Bozzelli et al., 1980
New York					
New York City	June 27-28, 1974 Aug 18-27, 1978[b]	9.75 (0.0661) 10.61 (0.0721)	1.0 (0.006) 0.16 (0.001)	4.5 (0.030) 1.00 (0.006)	Lillian et al., 1975 Evans et al., 1979
Niagara Falls and Buffalo	Fall 1978	2.0 (0.014)	0.02 (0.122 x 10^{-3})	1.0 (0.0068)	Pellizzari et al., 1979b
Whiteface Mtn.	Sept. 17, 1974	0.19 (12.8 x 10^{-4})	0.02 (0.13 x 10^{-3})		Lillian et al., 1975
Ohio[a]					
Wilmington	July 16-26, 1974			0.15 ± 0.015	Lillian et al., 1975
Texas					
Houston	Sept 16-25, 1978[b]	4.52 (0.030)	<0.1 (<0.001)	0.11 (0.001)	Evans et al., 1979
Aldine[a]	June 22-Oct. 20, 1977	0.037	0	0.012	Pellizzari et al., 1979
Deer Park[a]	July 29-30, 1976	0.15	0.01	0.07	Pellizzari et al., 1979
El Paso[a]	April 5-May 1, 1978	0.39	0.11	0.15	Pellizzari, 1979
Freeport[a]	Aug. 9, 1976			0.12	Pellizzari et al., 1979
Houston[a]	July 27, 1976- May 24, 1980	1.3	0	0.33	Pellizzari et al., 1979; Singh et al., 1980

TABLE 3-2. (continued)

Location	Date of Measurement	Reported Concentration, ppm (mg/m^3) Maximum	Minimum	Average	Reference
Texas					
LaPorte[a]	Aug. 12-13, 1976			0.49	Pellizzari et al., 1979
Pasadena[a]	July 28, 1976			0.003	Pellizzari et al., 1979
Utah[a]					
Magna	Oct. 24-Nov. 3, 1977	0.012	0	0.004 ± 0.006	Pellizzari, 1979
Washington[a]					
Auburn	Jan. 10-11, 1977	0.76	0.18	0.59 ± 0.27	Battelle, 1977
West Virginia[a]					
Charleston	Sept. 27-Nov. 20, 1977	0.16	0	0.004 ± 0.008	Pellizzari, 1978
St. Albans	Sept. 27-Oct. 25, 1977	0.064	0	0.016 ± 0.032	Pellizzari, 1978

[a] Data obtained from summary report of Brodzinsky and Singh, 1982. Values reported are 24-hour sampling concentrations.

[b] 24-hour value.

[c] Sampling time: 14 minutes.

[d] Sampling time: 100 minutes.

Some of the highest air levels of PCE reported have been associated with waste disposal sites. Pellizzari (1978) reported levels to ranges at sites in New Jersey that ranged from trace amounts to a maximum of 58 ppb (0.394 mg/m^3) in a 14-minute sampling period. PCE was adsorbed using Tenax cartridges.

Coefficients of variation for most of the recent studies reported by Singh et al. have been less than 30 percent.

Howie (1980) reported ambient air levels of PCE in the vicinity of laundries to be as high as 32 ppb (0.22 mg/m^3). In this study of indoor PCE concentrations, outdoor samples provided background data. Measurements were made by adsorbing PCE onto charcoal filters, followed by desorption with carbon disulfide and quantification by GC-ECD and GC-MS. Outdoor samples were collected for 24 hours. Of 124 measured samples, 56 had 24-hour levels of less than 1 ppb. Replicate sample analyses were reported to give an overall precision of better than 20 percent for both indoor and outdoor samples.

3.6.1.2 Water--Various studies have shown that PCE is found in both natural and municipal waters. A review by Deinzer et al. (1978) has summarized many of the findings. Love and Eilers (1982), in their review, reported that halogenated solvents such as PCE are seldom detected in concentrations greater than a few micrograms per liter in surface waters.

3.6.1.2.1 Natural waters. Surface waters, such as rivers and lakes, are the most important sources of drinking water in the United States. Attempts have been made to show an epidemiological link between the presence of halogenated organic compounds in drinking water and cancer (Harris and Epstein, 1976) but a cause-effect relationship has not been established.

Dowty et al. (1975a,b) detected PCE by GC-MS techniques in untreated Mississippi River water as well as in treated water. An approximate six-fold reduction in concentration occurred after sedimentation and chlorination. Tetrachloroethylene in water from a commercial deionizing charcoal filtering unit showed a marked increase over the amount found in finished water from treatment facilities or commercial sources of bottled water. The value of charcoal filtering to remove organics from water requires further study.

Suffet et al. (1977) reported detection of PCE in river waters supplying drinking water to Philadelphia, Pennsylvania. The Belmont Water Treatment Plant, with an average capacity of 78 million gallons per day, obtains influent from the Schuykill River.

In a study designed to detect pollutants in surface water at different U.S. sites, Ewing et al. (1977) identified PCE among the pollutants. Detection limits were not reported. The highest level (45 μg/l) was reported for surface water in Ashtabula, Ohio, located along the south edge of Lake Erie. In the vicinity of Philadelphia, 3 μg/l was detected. Less than 1 μg/l was reported along the Ohio River and at the confluence of its tributaries. Similarly, 1 μg/l or less was reported for all sites sampled in the Great Lakes and at six sites along the Tennessee River. An exception was Chattanooga where 13 μg/l was reported. In the greater Chicago area, the highest level found was 5 μg/l. In all samples taken in California, Oregon, and Washington, PCE was either not detected or was found at a concentration of 1 μg/l or less. Sampling sites included those in the vicinity of Los Angeles Harbor, Santa Monica Bay, and San Francisco Bay, at three sites along the Willamette River in Oregon, and two in the Puget Sound area.

Tetrachloroethylene was among a number of halogenated organics found in community drinking water supply wells in Nassau County, New York. Because contamination, 16 of these wells were closed by the New York State Health Department (Ewing et al., 1977). The maximum detected level of PCE in the contaminated wells was 375 μg/l. Since PCE is generally not used as a cesspool cleaning agent, previous industrial dumping may be the source of contamination.

Pearson and McConnell (1975) found an average PCE concentration of 0.12 ppb in Liverpool Bay sea water; the maximum concentration found was 2.6 ppb. Sediments from Liverpool Bay were found to contain 4.8 ppb (w/w). No direct correlation was found between PCE concentration in sediments and in the waters above. Rainwater collected near an organochlorine manufacturing site was found to contain 0.15 ppb (w/w) PCE (Pearson and McConnell, 1975); it was not detected in well waters. Upland waters of two rivers in Wales were found to contain approximately 0.15 ppb PCE; similar levels of trichloroethylene were found (Pearson and McConnell, 1975).

Löchner (1976) found that levels of PCE in Bavarian lake waters ranged from 0.015 to 3 ppb (0.015×10^{-3} to 2.7×10^{-3} mg/l). European surface waters were reported to have uniform PCE concentrations ranging from 0.2×10^{-3} to 0.002 mg/l. Analyses of river, canal, and sea water, all containing effluent from production and user sites in four countries, revealed PCE concentrations ranging from 0.01 to 46 ppb (0.01 to 46 μg/liter) (Correia et al., 1977).

3.6.1.2.2 Municipal waters. Bellar et al. (1974) measured the concentration of PCE in water obtained from sewage treatment plants in several cities. Before treatment, the average PCE concentration was 6.2 μg/l. The treated water before chlorination contained 3.9 μg/l PCE. After chlorination, the effluent contained 4.2 μg/l PCE.

Tetrachloroethylene has been detected in the drinking water of a number of U.S. cities. These include Evansville, Indiana (Keith et al., 1977); Kirkwood, Missouri (Keith et al., 1977); New Orleans, Louisiana (Dowty et al., 1975); Jefferson Parish, Louisiana (Dowty et al., 1975b); Cincinnati, Ohio (Keith et al., 1977); Miami, Florida (Keith et al., 1977); Grand Forks, North Dakota (Keith et al., 1977); Lawrence, Kansas (Keith et al., 1977); New York City (Keith et al., 1977); and Tucson, Arizona (Keith et al., 1977).

Concentrations recorded for the above cities were less than 1 μg/l. An exception was Jefferson Parish, which had a measured concentration of 5 ppb (5 μg/l). Keith et al. (1977) did not detect PCE in the drinking water of Philadelphia. Tetrachloroethylene was found in Evansville tap water from July 1971 to December 1972. The Ohio River Basin, a heavily industralized area, is upstream from Evansville and serves as a major source of drinking water for that community.

Dowty et al. (1975b) determined levels of PCE in the drinking water for New Orleans. Considerable variation in the relative concentrations of the various halogenated compounds was observed from day to day.

Contamination of drinking water by PCE was recently investigated by Wakeham et al. (1980). It was reported that elevated concentrations of PCE were found in drinking water transported in vinyl-coated asbestos-cement pipes in areas of the town of Falmouth, Massachusetts. Tetrachloroethylene is used as a solvent during the application of the vinyl coating to the pipe during manufacturing. It was suggested that residual solvent leaches into the water carried in these pipes.

Using a charcoal trap with flame ionization detection, Wakeham and coworkers (1980) detected levels ranging from 140 to 18,000 ppb in unflushed pipes. In other parts of the distribution system, levels were less than 2 ppb. The authors reported that vinyl-coated asbestos-cement pipe has been used in parts of the northeastern United States over the past decade in response to concerns that water carried in uncoated pipes could contain asbestos fibers.

In municipal waters supplying the cities of Liverpool, Chester, and Manchester, England, 0.38 ppm (w/w) PCE was found (Pearson and McConnell, 1975).

Munich (Germany) drinking water was analyzed by Löchner (1976). Samples taken at various sampling points and times gave a range of 1.1×10^{-3} to 2.4 x

10^{-3} mg/l. Raw sewage at Munich contained 0.088 mg/l PCE. On mechanical clarification, the 24-hour average concentration of PCE was 0.0068 mg/l.

3.7 ANALYTICAL METHODOLOGY

Tetrachloroethylene has been analyzed in air and in water, as well as in biological fluids, by a variety of methods. Separation of PCE from other compounds is usually carried out by gas chromatography (GC). Quantification is usually made by either electron capture detection (ECD) or mass spectroscopy (MS). These analytical methods, GC/ECD or GC/MS, have a lower limit of detection of a few ppt.

3.7.1 Ambient Air

Because PCE levels in air are typically in the sub-ppb range, the sampling and analysis techniques have been designed to detect trace gas levels.

3.7.1.1 Sampling and Sources of Error--Because of the low levels occurring in ambient air, sampling techniques have focused on adsorption onto solids such as charcoal (Evans et al., 1979) or on concentration methods that increase the amount of PCE to above detection limits (Rasmussen et al., 1977). In the upper troposphere, PCE has been sampled by pumping air into stainless steel or glass containers until there is a positive pressure relative to the surrounding atmosphere (Singh et al., 1979).

Evans et al. (1979) sampled PCE using a method based on adsorption onto activated charcoal, followed by desorption by carbon disulfide/methanol. The precision of the analytical method, expressed as a coefficient of variation for the total measurement system (including sample collection, handling, and preparation) was reported as 16 percent. When 49 quality control samples were analyzed, the overall percent recovery from the charcoal tubes was 70.2 ± 1.7 percent. When the total measurement system was independently checked by using Tenax GC, another solid adsorbent, the paired data were correlated with a coefficient of 0.82, with the average Tenax result exceeding the average charcoal result by 21 percent. Samples were in the sub- to low-ppb range. Evans et al. (1979) reported that PCE is stable on charcoal tubes for at least one month at 0°C. The lower limit of detection for the total measurement method (to include GC/ECD) was estimated at 0.68 $\mu g/m^3$ (0.1 ppb).

Pellizzari and Bunch (1979) reported the use of Tenax GC, a porous polymer based on 2,6-diphenyl-p-phenylene oxide, to adsorb PCE from ambient air. Recovery was made by thermal desorption and helium purging into a freezeout trap. The estimated detection limit, when high resolution GC/MS is used, is 0.38 ppt (2.5×10^{-6} mg/m^3). Accuracy of analysis was reported at ± 30 percent. Included among the inherent analytical errors were (1) the ability to accurately determine the breakthrough volume, (2) the percent recovery from the sampling cartridge after a period of storage, and (3) the reproducibility of thermal desorption from the cartridge and its introduction into the analytical system. To minimize loss of sample, cartridge samplers should be enclosed in cartridge holders and placed in a second container that can be sealed, protected from light, and stored at 0°C. The advantages reported for Tenax include (1) low water retention, (2) high thermal stability, and (3) low background levels (Pellizzari, 1974, 1975, 1977; Pellizzari et al., 1976). Singh et al. (1982) have cautioned that Tenax suffers from serious artifact problems.

Krost et al. (1982) reported an estimated detection limit of 0.3 ppt for PCE using high resolution GC/MS. The detection limit was calculated on the basis of the breakthrough volume for a known amount of Tenax GC at 10°, 21°, and 32°C. Field sampling and analysis precision of the Tenax method was found to range from ± 10 to ± 40 percent relative standard deviation for different substances when replicate field sampling cartridges were examined.

Knoll et al. (1979) reported resolution of PCE from other chlorinated hydrocarbons with Carbopak C-HT, a graphitized thermal carbon black treated with hydrogen at 1000°C. Carbowax 20M, reacted with nitroterephthalic acid, was reported not to give good separation. Porapak T, a porous polymer based on ethylene glycol dimethacrylate, was reported to give good separation.

A freezeout concentration has been developed by Rasmussen and coworkers (1977) to determine trace levels of PCE in the presence of other compounds. The detection limit was reported at 0.2 ppt (1.36×10^{-6} mg/m^3) for 500-ml aliquots of ambient air samples measured by GC coupled with EDC. When freezeout is complete, PCE remains behind, and such gases as oxygen and nitrogen are passed through as the freezeout loop is heated. The carrier gas sweeps the contents onto the column.

Singh et al. (1979, 1982) have employed the cryogenic trapping of air containing trace levels of PCE and other compounds of interest. During sampling, traps are maintained at liquid oxygen temperature. Traps were made of stainless steel packed with a 4-inch bed of glass beads or glass wool. Aliquots are thermally desorbed and injected directly into the gas chromatograph. Both electric heating and hot water desorption techniques were found to be satisfactory.

Makide et al. (1980) employed stainless steel canisters for sampling of air containing PCE at levels of about 20 ppt. Canisters were polished electrochemically. Canisters were evaluated to 10^{-4} Pa at 200°C before sampling. The composition of the samples was reported to have remained unchanged for over a year.

The monitoring method recommended by the National Institute for Occupational Safety and Health (1977) utilizes adsorption onto charcoal followed by desorption with carbon disulfide. This method is recommended for the range 96 to 405 ppm (655 to 2749 mg/m^3). The coefficient of variation for the analytical and sampling method is 0.052. A reported disadvantage is that the charcoal may be overloaded, thus limiting the amount of sample that can be collected. This may be obviated by using more than one adsorber.

Budde and Eichelberger (1979) reported that carbon adsorption methods generally have more disadvantages than those methods using porous polymers. The advantage of porous polymers coupled with thermal desorption, as contrasted with solvent desorption, is higher sensitivity, because the total sample is measured and there is no background from the solvent. However, because the total sample is measured, multiple samples must be collected to insure against accident and loss of sample, and to obtain information on the precision of the method. Tenax GC was reported to be superior to other polymers for organics analysis. Samples are taken by pulling air through glass tubes packed with Tenax GC, 60/80 mesh and supported by plugs of glass wool. After a suitable sampling period (about 2 to 4 hours in urban areas), tubes are capped and stored. Samples are thermally desorbed (250 to 270°C) for 3 minutes under a 10-ml helium flow.

Criteria for evaluating methods using solid sorbents to collect organic compounds from air have been discussed by Melcher et al. (1978). Among the factors to be considered are effects of (1) size of collection tube (2) breakthrough volume, (3) humidity, (4) temperature, (5) migration, (6) desorption efficiency, and (7) concentration.

3.7.1.2 Analysis--The sampling methods which use solid adsorbents or cryogenic techniques have the trap connected to the gas chromatograph by multiple-port gas sampling valves. With solid traps, the collected organics are quickly heated and the desorbed organics are passed through capillary columns. A number of coating materials in the capillary columns have been successfully used for separating PCE. These materials include (1) SF-96 on 100/120 mesh

Chromosorb W (Cronn et al.,1977); (2) SP-2100 on 80/100 mesh Supelcoport (Singh et al., 1979); (3) 80/100 mesh Carbopak C-HT, Porapak T, and SP-2100/0.1 percent Carbowax 1500 on 100/ 120 mesh Supelcoport (Knoll et al., 1979). In the method used by Evans et al. (1979) in field studies, a 1.8-m glass column with a 2-mm i.d., packed with 0.1 percent SP-1000 on Carbopack C, 80/100 mesh was used to separate PCE from other organics in ambient air samples. Twenty-four-hour samples were adsorbed onto charcoal. After desorption with carbon disulfide/ methanol, a 1.0-µl aliquot was injected into the gas chromatograph. The separation conditions included an oven temperature of 125°C (all transfer lines at least 170°C), and the carrier gas was 5 percent methane in argon. Quantification was made by ECD (Nickel 63; ECD temperature of 218°C) and a standing current of 0.5 amperes. To insure that the cell was not contaminated, the sensitivity of the detector was evaluated by comparing the standing current with the pulse frequency curve.

Electron capture detection is a method of choice used by a number of investigators (Singh et al., 1977, 1979, 1982; Rasmussen et al., 1977). Singh et al. (1979) maintained the ECD at a higher temperature (325°C) than did Evans et al. (1979), because it was found that the ECD response increased with an increase in temperature. The identity of PCE was confirmed by determining its ionization efficiency as well as the EC thermal response.

More recently, Singh et al. (1982) maintained the ECD at 275°C with a carrier flow rate of 40 ml/min to analyze for PCE and 11 other halogenated organics in ambient air. Identity of PCE and other compounds was established from retention times on multiple columns, the ECD thermal response, and the ECD ionization efficiency. Lillian and Singh (1974) reported that the accuracy associated with GC-ECD measurements of compounds having ionization efficiencies exceeding 50 percent is 75 percent or greater. Using two ECDs in series, PCE was found to have an ionization efficiency of 70 percent. In a comparison of GC-ECD with GC-MS, Cronn et al. (1976) judged GC-ECD to be superior in reproducibility for quantitating halocarbons. Of four halocarbon standards (PCE not among them) measured by GC-ECD, the coefficients of variation ranged from 1.4 to 4.3 percent, compared to a range of 4 to 19 percent when 11 halocarbon standards were measured by GC-MS. A close agreement between the levels of PCE and other halocarbons determined by GC-ECD and GC-MS on the same ambient air samples was obtained by Russell and Shadoff (1977).

GC-ECD was used by Pellizzari et al. (1979) to measure PCE in ambient air samples. Samples were adsorbed onto charcoal and desorbed with a mixture of methanol and carbon disulfide, and aliquots were separated on a 2.5-mm (i.d.) Pyrex column containing 0.2 percent Carbowax 1500 on Carbopack C. The estimated detection limit was 2.5 x 10^{-6} mg/m^3 (0.38 ppt).

Makide et al. (1980) separated trace levels of PCE from other halogenated organics on a silicone OV-101 column (10 percent by weight coated on Chromosorb W-HP, 80-100 mesh) of 5-mm i.d. and 3 m long. Samples were transferred to the column cooled at -40°C during preconcentration. Separation was carried out by raising column temperature 5°C per minute up to 70°C. Methane was added to the carrier gas (nitrogen) to improve the signal-to-noise ratio and to stabilize the baseline. Quantification was made by a constant-current ECD. The detection limit for PCE was reported as <0.05 ppt. Precision was reported to be within 2 percent.

To measure PCE at levels expected to occur in occupational air, flame ionization detection has been used. The analytical method S335, suggested by the National Institute for Occupational Safety and Health (1977) for organic solvents in air, utilizes adsorption onto charcoal, followed by desorption with carbon disulfide. PCE is separated by GC. The method is recommended for the range 96 to 405 ppm (655 to 2749 mg/m^3). The coefficient of variation for the analytical sampling method is 5.2 percent. With the method, interferences are minimal, and those that do occur can be eliminated by altering chromatographic conditions.

3.7.2 Water

3.7.2.1 Sampling--A variety of techniques and methods are commonly used to sample trace levels of PCE and other halogenated organics in water samples. Coleman et al. (1981) have reported that the Grob closed-loop-stripping technique is an excellent tool to monitor organics in water at the ppt level. It was reported that a million-fold concentration of most low and intermediate molecular weight organics can be achieved. Quantitation is performed by spiking the initial water sample with a series of internal standards, stripping at 30°C for two hours, and by chromatographing the CS_2 extract on a wall-coated open-tubular capillary.

3.7.2.1.1 Gas purging and trapping. In this method, finely divided gas bubbles are passed through the sample, transferring the organic compounds to the gas phase. The gas is then passed through a solid adsorbent in a trap. Compounds are desorbed at elevated temperature by backflushing with a carrier gas into the gas chromatograph (Budde and Eichelberger, 1979). Since the boiling point of PCE is 121°C, Tenax GC would be an effective absorbent.

The purge and trap procedure is widely used, as is the purging device developed by Bellar and Lichtenberg (1974). For most organic compounds, detection limits as low as 1 µg/l can be obtained when GC/MS is used for analysis. Mieure (1980) reported that adding salt to the sample or increasing its temperature dramatically improves the removal of most organic compounds.

Otson and Williams (1982) have described a modified purge and trap technique for evaluation of volatile organic pollutants in water. The detection limit reported for PCE was 0.1 µg/l with ECD, and 1 µg/l with flame ionization detection (FID). Tenax GC was used as packing for the combined trap/chromatographic column.

3.7.2.1.2 Headspace analysis. This method describes static sampling of the vapor phase that is in equilibrium with the aqueous sample. The concentration in the headspace is proportional to the concentration in the water (Kepner et al., 1964). In this procedure, trace organics in the range of 10 to 100 µg/l can be sampled (Mieure, 1980). Mieure (1980) reported a detection limit for PCE (analyzed by ECD) of 0.01 µg/l. With flame ionization detection, the limit was 32 µg/l. Typically, a 1- to 2-ml sample of the headspace is removed and injected into the gas chromatograph. Headspace extraction coupled with mixed column separation and ECD analysis was reported by Castello et al. (1982) to be suitable for rapid screening of drinking water supplies.

3.7.2.1.3 Liquid/liquid extraction. Mieure (1980) reported that recovery of PCE from water spiked with 2.3 to 90 µg/l ranges from 100 to 113 percent. The precision ranges from 10 to 12 (RSD). These results were obtained from a round-robin study, by the American Society for Testing and Materials (ASTM) Committee D19 on Water, using liquid/liquid extraction. The extractant was not identified.

Budde and Eichelberger (1979) cautioned that a disadvantage to this method is that very volatile compounds may be lost during extract concentration or during solvent elution from the gas chromatograph. Methylene chloride was recommended as the only general-purpose solvent.

Sheldon and Hites (1978) used methylene chloride in a sampling procedure applied to the identification of PCE and 98 other organic compounds in river water. Grab samples were collected in amber glass bottles and samples for solvent extraction were immediately preserved by acidifying to pH 2 with hydrochloric acid and by adding 250 ml of methylene chloride. The analytical techniques used were those reported by Jungclaus et al. (1978). Solvent extraction efficiencies were not determined. While PCE was previously detected in vapor stripping analysis of prior samples, it was not detected in the water samples cited in their report.

3.7.2.2 Analysis--Schwarzenbach et al. (1979) used ECD to measure PCE levels in water samples. Volatile organics were purged and adsorbed onto charcoal. Desorption was by carbon disulfide. Quantification was made by FID and ECD.

Dowty et al. (1975a) used Tenax GC in trapping purgeable organics from water samples. The polymer containing the trapped organics was placed in the GC injection port maintained at 200°C. Final separation was made on a glass capillary column coated with Pluronics 121. The effluent of the column was split to allow for FID and ECD.

3.7.3 Biological Media

Ramsey and Flanagan (1982) have described a gas chromatographic method reported to be suitable for analysis of PCE and other organics present in blood. Detection was both by flame ionization and ECD. Approximately 200 µl of blood or 200 mg tissue is required for analysis.

3.7.4 Calibration

Singh et al. (1982) found that primary standards of PCE in the low-ppb range could be satisfactorily calibrated using permeation tubes maintained either at 30° or 70°C. Permeation tubes were standard FEP or TFE Teflon. All permeation tubes were conditioned for two weeks or longer. Errors in the permeation rate were ± 10 percent. Singh et al. (1982) found that long-term (2 years) stability of primary standards (10 ppm) of PCE in aluminum containers was excellent.

3.7.5 Storage and Stability of PCE

Sampling of exhaled breath commonly is accomplished by use of Saran bags or glass pipettes. Temperature and storage time of the samples before analysis are factors to be considered in obtaining accurate data.

3.7.5.1 Glass Sampling Tubes--Evaluation of glass sampling tubes was made by Pasquini (1978). Serial alveolar breath samples were collected in the tubes and the concentrations of PCE were analyzed by a gas chromatograph equipped with a flame ionization detector. Analysis of vapor retention over 169 hours indicated that glass tubes can be acceptable containers for breath samples if precautions are taken. Moisture, temperature, and tube surface and condition can greatly alter vapor retention.

In tubes filled with breath samples taken at room temperature and also stored at room temperature, the mean percent loss of PCE was 64.8 ± 9.4. Partitioning of PCE between the vapor and liquid states appears to be a reasonable explanation for vapor retention loss. It was shown for trichloroethylene that if storage tubes were maintained at 37°C, vapor retention was greater. It was also greater if siliconized tubes were used.

3.7.5.2 Saran, Teflon and Tedlar Containers--Saran bags as storage containers for PCE vapors have been evaluated by Desbaumes and Imhoff (1971). Although it was concluded that Saran can be an acceptable container, the diffusion rate was appreciable over a 24-hour storage period. Storage temperature was not reported.

Teflon containers were judged by Drasche et al. (1972) to be more suitable than Saran even though losses of PCE due to adherence to Teflon surfaces were appreciable. Within the first 30 minutes after introduction of a mixture (relative humidity = 45 percent) of benzene, trichloroethylene, and PCE into a Teflon bag, vapor concentrations of each dropped 40 to 60 percent. However, when the bag was heated to 100°C for 30 minutes after the mixture had been stored for 44 hours at 25°C, concentrations rose to the initial values.

Knoll et al. (1979) reported that PCE, when stored at ambient temperatures for 10 days or less in Tedlar bags, was stable. When the vapor mixture is heated to 70°C, PCE is stable for no more than 5 hours.

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4. ECOSYSTEM CONSIDERATIONS

4.1 EFFECTS ON AQUATIC ORGANISMS AND PLANTS

Tetrachloroethylene (PCE) has been tested for acute toxicity in a limited number of aquatic species. The information presented in this chapter presents observed levels reported to result in adverse effects under laboratory conditions. It is recognized that such parameters of toxicity are not easily extrapolated to environmental situations. Test populations themselves may not be representative of the entire species, in which susceptibility of various life-stages to the test substance may vary considerably. Guidelines for the utilization of these data in the development of criteria levels for PCE in water are discussed elsewhere (U.S. EPA, 1979).

The toxicity of PCE to fish and other aquatic organisms has been gauged principally by flow-through and static testing methods (Committee on Methods for Toxicity Tests with Aquatic Organisms, 1975). The flow-through method exposes the organism(s) continuously to a constant concentration of PCE while oxygen is continuously replenished and waste products are removed. A static test, on the other hand, exposes the organism(s) to the added initial concentration only. Both types of tests are commonly used as initial indicators of the potential of substances to cause adverse effects.

4.1.1 Effects on Freshwater Species

Alexander et al. (1978) used both flow-through (measured) and static (unmeasured) methods to investigate the acute toxicity of four chlorinated solvents, including PCE, to adult fathead minnows (*Pimephales promelas*). Studies were conducted in accordance with test methods described by the Committee on Methods for Toxicity Tests with Aquatic Organisms (1975).

The static and flow-through results for the 96-hour experiments indicated that PCE was the most toxic of the solvents tested. The lethal concentration (96-hour LC_{50}) necessary to kill 50 percent of the fathead minnows in the flow-through test was 18.4 mg/l (18.4 ppm); the 95 percent confidence limits were 14.8 to 21.3 mg/l (14.8 to 21.3 ppm). In comparison, the static experiments gave a 96-hour LC_{50} of 21.4 mg/l (21.4 ppm); the 95 percent confidence limits were 16.5 to 26.4 mg/l (16.5 to 26.4 ppm). Fish affected during exposure were transferred to static freshwater aquaria at the end of exposure. Only those fish severely affected by high concentrations did not recover.

When the minnows were exposed to sublethal levels for short exposure intervals, only reversible effects were observed. Endpoints evaluated were loss of equilibrium, melanization, narcosis, and swollen, hemorrhaging gills. The effective flow-through concentration (EC_{50}) of PCE that produced one or more of these reversible effects was 14.4 mg/l (14.4 ppm).

The 96-hour LC_{50}, in a static test with the bluegill (Lepomis macrochirus), was reported as 12.9 mg/l (12.9 ppm) (U.S. EPA, 1978, 1980). The most sensitive species tested is the rainbow trout (Salmo gairdneri). The LC_{50} determined by a flow-through measured procedure was 5.28 mg/l (5.28 ppm) (U.S. EPA, 1980). With embryo-larval test procedures, a chronic value of 0.840 mg/l (0.840 ppm) was obtained by the U.S. EPA (1980) for the fathead minnow.

With the freshwater invertebrate Daphnia magna, a 48-hour EC_{50} value of 17.7 mg/l (17.7 ppm) was obtained (U.S. EPA, 1980). The midge Tanytarsus dissimilis was more resistant, with a 48-hour LC_{50} value of 30.84 mg/l (30-84 ppm) determined under static, measured conditions.

4.1.2 Effects on Aquatic Plants

As cited in the U.S. EPA Ambient Water Quality Criteria Document (U.S. EPA, 1980), no adverse effects on chlorophyll a or cell numbers of the freshwater alga Selenastrum capricornutum were observed at exposure concentrations as high as 816 mg/l (816 ppm).

For the saltwater species Skeletonema costatum a 96-hour EC_{50} of about 500 mg/l (500 ppm) was determined for effects on chlorophyll a and cell number. This alga species is more resistant than the alga Phaeodactylum tricornutum for which the EC_{50} value was determined to be 10.5 mg/l (10 ppm) (Pearson and McConnell, 1975).

4.1.3 Effects on Saltwater Species

Pearson and McConnell (1975) investigated the acute toxicity of PCE on the dab (Limanda limanda), barnacle larvae (Barnacle nauplii), and on unicellular algae (Phaeodactylum tricornutum). The LC_{50} was 5 mg/l (5 ppm) for the dab. The 48-hour LC_{50} for barnacle larvae was 3.5 mg/l (3.5 ppm).

Toxicity to the unicellular alga was assessed by measuring alterations in the uptake of carbon from atmospheric carbon dioxide during photosynthesis. Uptake of carbon dioxide was measured by the use of sodium-^{14}C-carbonate. The EC_{50} was 10.5 mg/l (10.5 ppm).

Data collected by the U.S. Environmental Protection Agency (1980) indicate that, for mysid shrimp (Mysidopsis bahia), the LC_{50} was 10.2 mg/l (10.2 ppm) in a 96-hour static, unmeasured procedure. Chronic testing over the life cycle of the mysid shrimp resulted in a chronic value of 0.450 mg/l (0.45 ppm) (U.S. EPA, 1980). The chronic value is 0.044 times the 96-hour LC_{50}.

4.2 BIOCONCENTRATION AND BIOACCUMULATION

An indicator of the potential for a substance to result in cumulative or chronic toxic effects in aquatic species is the bioconcentration factor (BCF). Bioconcentration refers to the increased concentration of a substance within an organism (e.g., fish) relative to the ambient water concentration under steady-state conditions. As defined by Veith et al. (1979), the bioconcentration factor is a constant of proportionality between the concentration of the chemical in fish and in the water. This can be more clearly expressed as

$$\frac{C_f}{C_w} = \frac{K_1}{K_2} = K_{BCF} \quad \text{at steady state.} \quad (4\text{-}1)$$

Bioaccumulation, a term often erroneously used in place of bioconcentration, can be defined as that process which includes bioconcentration and any uptake of toxic substances through consumption of one organism by another. The BCF alone, however, may not be the most useful measure of the overall fate of a substance in water or of its potential for producing toxic effects, for all chemicals.

In the absence of direct measurement, a measure commonly used to assess the degree to which a compound may be bioconcentrated is the octanol-water partition coefficient. Estimates for the octanol/water partition coefficient range from 339 to 871 (Neely et al., 1974; U.S. EPA, 1980; Chiou et al., 1977). The partition coefficient has been shown to be directly related to bioconcentration potential in fish (Neely et al., 1974). In guidelines recently set forth by the American Society for Testing and Materials (ASTM), a log partition coefficient exceeding a value of three was considered an indication of a high probability of measurable bioaccumulation in aquatic species (ASTM, 1978). Compounds that exhibit a large log coefficient generally are those with low water solubility and high solubility in organic solvents. Although a compound may demonstrate a high BCF or log partition coefficient, other environmental factors that act to reduce this potential often exist. The compound may be rapidly hydrolyzed or degraded by other mechanisms. Measurable uptake by the organism may be precluded if the tissue depuration rate for the substance is great.

With regard to PCE, the BCF was calculated to be 34 and 49 in two fish species (U.S. EPA, 1980; Neely et al., 1974). Neely et al. (1974) found that the BCF for PCE and other chemicals was linearly related to the respective partition coefficients. For PCE, the log partition coefficient was 2.88, and the BCF, determined in trout (rainbow) muscle, was 39.6 ± 5.5. The trout were exposed to two undefined levels of PCE for an undefined period of time. The extent to which the levels approached the acute LC_{50} level for this species or whether a steady-state was achieved was not reported. Preliminary data in the U.S. Environmental Protection Agency study (1980) with bluegill indicated a BCF of 49. The log partition coefficient was 2.53. The depuration rate was rapid, with a half-life of less than one day.

Although these studies suggest that PCE does have bioconcentration potential, the extent to which this potential can be manifested in the form of adverse effects can be gauged only from the results of toxicological studies.

4.2.1 Levels of PCE in Tissues of Aquatic Species

Pearson and McConnell (1975) suggested that chronic and sublethal effects of PCE may result from exposure to low concentrations of PCE, if the halocarbon can be bioaccumulated. As a first step in addressing the question of bioaccumulation, these investigators determined levels of PCE in a variety of invertebrate and vertebrate species (Tables 4-1 and 4-2).

Among marine invertebrates, wet tissue concentrations of PCE were found to range from 0.001 to 0.009 ppm. The highest concentration (0.008 to 0.009 ppm) found was in the crab (*Cancer pagurus*). Higher levels were found in marine algae (0.013 to 0.022 ppm). In tissues of fish, a range of 0.0003 to 0.041 ppm was found. Concentrations in the livers of three species of fish were found to greatly exceed those found in the flesh. Tissue levels from all species are shown in Table 4-1. Concentrations reported for fish-eating birds and marine mammals were for selected tissues such as fish liver, sea bird eggs, and seal blubber. If the reported tissue concentrations for birds and mammals are converted to a whole-body weight basis, concentrations are much lower and closer to concentrations measured in seawater, indicating little or no bioconcentration and biomagnification (U.S. EPA, 1981).

TABLE 4-1. LEVELS OF PCE IN TISSUES OF MARINE ORGANISMS, BIRDS, AND MAMMALS

Species	Source	Tissue	Trichloroethylene[a] (ppm x 10^3)	PCE (ppm x 10^3)
Invertebrates				
Plankton	Liverpool Bay	-	0.05 - 0.4	0.05 - 0.5
Plankton	Torbay	-	0.9	2.3
Ragworm (*Nereis diversicolor*)	Mersey Estuary	-	Not detected	2.9
Mussel (*Mytilus edulis*)	Liverpool Bay	-	4 - 11.9	1.3 - 6.4
	Firth of Forth	-	9	9
	Thames Estuary	-	8	1
Cockle (*Cerastoderma edule*)	Liverpool Bay	-	6 - 11	2 - 3
Oyster (*Ostrea edulis*)	Thames Estuary	-	2	0.5
Whelk (*Buccinum undatum*)	Thames Estuary	-	Not detected	1
Slipper limpet (*Crepidula fornicata*)	Thames Estuary	-	9	2
Crab (*Cancer pagurus*)	Tees Bay	-	2.6	2.3
	Liverpoool Bay	-	10 - 12	8 - 9
	Firth of Forth	-	15	7
Shorecrab (*Carcinus maenus*)	Firth of Forth	-	12	6
Hermit crab (*Eupagurus bernhardus*)	Firth of Forth	-	15	15
	Thames Estuary	-	5	2
Shrimp (*Crangon crangon*)	Firth of Forth	-	16	3

TABLE 4-1. (continued)

Species	Source	Tissue	Trichloroethylene[a] (ppm x 10^3)	PCE (ppm x 10^3)
Starfish (*Asterias rubens*)	Thames Estuary	-	5	1
Sunstar (*Solaster sp.*)	Thames Estuary	-	2	2
Sea Urchin (*Echinus esculentus*)	Thames Estuary	-	1	1
Marine Algae				
Enteromorpha compressa	Mersey Estuary	-	19 - 20	14 - 14.5
Ulva lactuca	Mersey Estuary	-	23	22
Fucus vesiculosus	Mersey Estuary	-	17 - 18	13 - 20
Fucus serratus	Mersey Estuary	-	22	15
Fucus spiralis	Mersey Estuary	-	16	13
Fish				
Ray (*Raja clavata*)	Liverpool Bay	flesh liver	0.8 - 5 5 - 56	0.3 - 8 14 - 41
Plaice (*Pleuronectes platessa*)	Liverpool Bay	flesh liver	0.8 - 8 16 - 20	4 - 8 11 - 28
Flounder (*Platyethys flesus*)	Liverpool Bay	flesh liver	3 2	2 1
Dab (*Limanda limanda*)	Liverpool Bay	flesh liver	3 - 5 12 - 21	1.5 - 11 15 - 30

TABLE 4-1. (continued)

Species	Source	Tissue	Trichloroethylene[a] (ppm x 10^3)	PCE (ppm x 10^3)
Mackerel (Scomber scombrus)	Liverpool Bay	flesh	5	1
		liver	8	not detected
Dab (Limanda limanda)	Redcar, Yorks	flesh	4.6	5.1
	Thames Estuary	flesh	2	3
Plaice (Pleuronectes platessa)	Thames Estuary	flesh	3	3
Sole (Solea solea)	Thames Estuary	flesh	2	4
		guts	11	1
Red gurnard (Aspitrigla cuculus)	Thames Estuary	flesh	11	1
		guts	6	2
Scad (Trachurus trachurus)	Thames Estuary	flesh	2	4
Pout (Trisopterus luscus)	Thames Estuary	flesh	2	2
Spurdog (Squalus acanthias)	Thames Estuary	flesh	3	1
Mackerel (Scomber scombrus)	Torbay, Devon	flesh	2.1	Not detected
Clupea sprattus	Torbay, Devon	flesh	3.4	1.6
Cod (Gadus morrhua)	Torbay, Devon	flesh	0.8	<0.1
		Air bladder	<0.1	3.6
Sea and Freshwater Birds				
Gannet (Sula bassana)	Irish Sea	liver	4.5 - 6	1.5 - 3.2
		eggs	9 - 17	4.5 - 26
Shag (Phalacrocerax aristotelis)	Irish Sea	eggs	2.4	1.4

TABLE 4-1. (continued)

Species	Source	Tissue	Trichloroethylene[a] (ppm x 10^3)	PCE (ppm x 10^3)
Razorbill (*Alca torda*)	Irish Sea	eggs	28 - 29	32 - 39
Kittiwake (*Rissa tridactyla*)	North Sea	eggs	33	25
Swan (*Cygnus olor*)	Frodsham Marsh	liver	2.1	1.9
		kidney	14	6.4
Moorhen (*Gallinula chloropus*)	Merseyside	liver	6	3.1
		muscle	2.5	0.7
		eggs	6.2 - 7.8	1.3 - 2.5
Mallard (*Anas platyrynchos*)	Merseyside	eggs	9.8 - 16	1.9 - 4.5
Mammals				
Grey Seal (*Halichoerus grypus*	Farne Island	blubber	2.5 - 7.2	0.6 - 19
		liver	3 - 6.2	0 - 3.2
Common Shrew (*Sorex araneus*)	Frodsham Marsh	-	2.6 - 7.8	1

[a] Levels for trichloroethylene included for comparative purposes.

Source: Pearson and McConnell, 1975.

TABLE 4-2. ACCUMULATION OF PCE BY DABS

Tissue	Period of Exposure (days)	Mean Exposure Concentration (ppm)	Mean Concentration in Tissue (ppm x 100)	Accumulation Factor
flesh	3 - 35	0.3	2,800[a] (13)	x 9
liver	3 - 35	0.3	113,000 (14)	x 400
flesh	3 - 35	0.03	60 (9)	x 5
liver	3 - 35	0.03	7,400[b] (9)	x 200
flesh	10	0.2	1,300 (7)	x 6
liver	10	0.2	69,000 (7)	x 350

Numbers in parentheses are number of specimens analyzed.

[a] One fish had a flesh concentration of 29.7 ppm and was omitted from calculations.

[b] One fish had flesh concentration of 50.3 ppm and was omitted from calculations.

Source: Pearson and McConnell, 1975.

The average concentration of PCE in seawater taken from Liverpool Bay, an area where many species of organisms were collected, was 0.00012 ppm. A comparison of this value with those presented in Table 4-1 indicates an uptake of as much as 75-fold. It was the authors' contention that, based on their observations, there is little indication that bioaccumulation occurs in the food chain.

As shown in Table 4-2, dabs (Limanda limanda) exposed to 0.3 ppm for 3 to 35 days were found to have a BCF (liver) for PCE of 400. It was not reported whether this period of exposure approximated a steady-state for PCE. After dabs were returned to clean seawater, the level of PCE dropped to 1/100 of the original level in 4 days and to 1/1000 of the initial level after 11 days (Figure 4-1). The ratio between liver and flesh concentrations is approximately 100 to 1. The relationship between flesh and liver concentrations in the dab is shown in Figure 4-2.

Dickson and Riley (1976) detected PCE in three species of mollusks and in five species of fish collected near Port Erin, Isle of Man. Levels of PCE in various tissues are shown in Table 4-3. Relative to the PCE concentration in seawater, there was only a slight enrichment in the tissues (< 25 times). Tetrachloroethylene had one of the lowest mean bioconcentration factors.

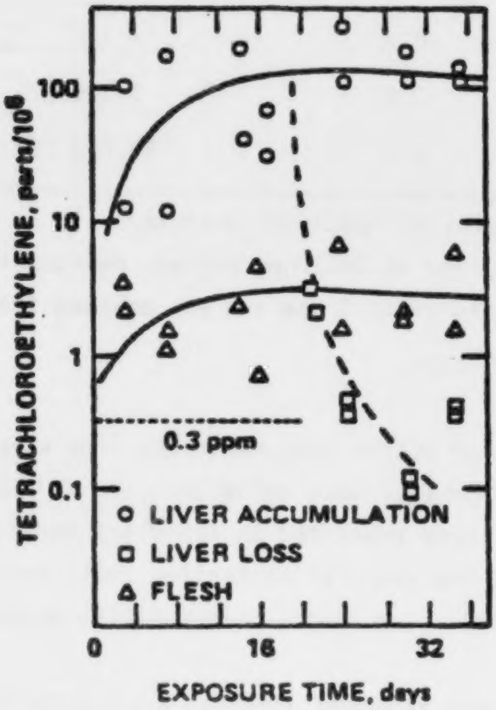

Figure 4-1. Accumulation and loss of PCE by dabs.

Source: Alexander et al., 1978.

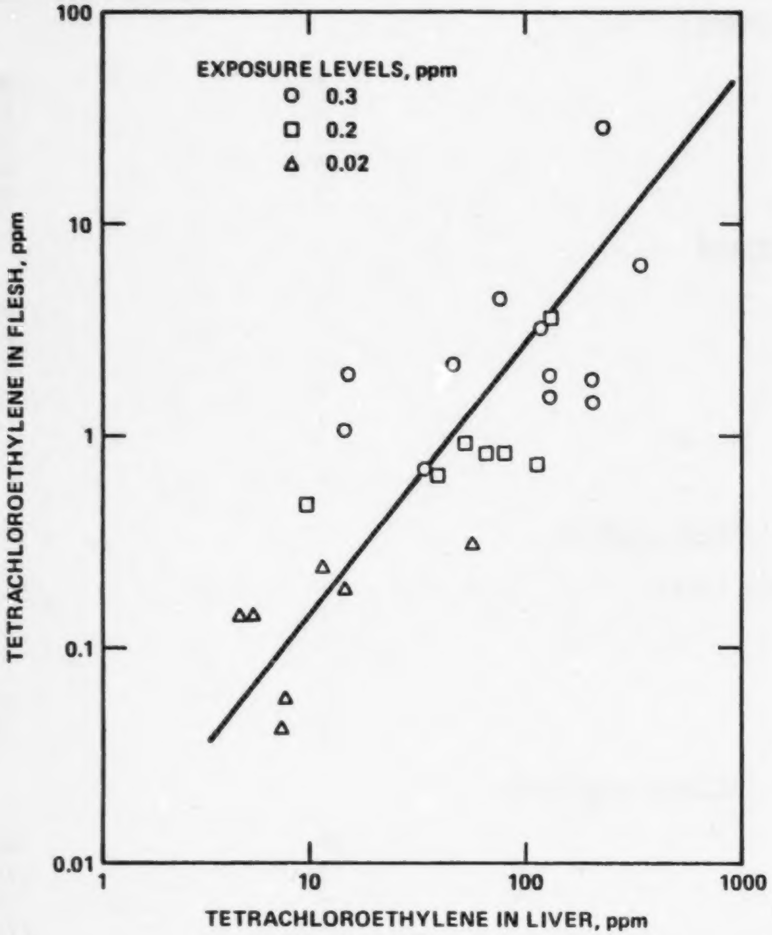

Figure 4-2. Relation between flesh and liver concentration of PCE in dabs.

Source: Alexander et al., 1978.

TABLE 4-3. CONCENTRATION OF PCE AND TRICHLOROETHYLENE IN MOLLUSKS AND FISH NEAR THE ISLE OF MAN

Species	PCE	Trichloroethylene
	(mg x 10^6/g dry weight tissue)	
Eel (*Conger conger*)		
brain	6	62
gill	2	29
gut	3	29
liver	43	43
muscle	1	70
Cod (*Gadus morhua*)		
brain	3	56
gill	-	21
heart	3	11
liver	8	66
muscle	2	8
skeletal tissue	-	-
stomach	6	7
Coalfish (*Pollachius birens*)		
alimentary canal	-	306
brain	-	71
gill	4	-
heart	-	-
liver	6	70
muscle	2	8
Dogfish (*Scylliorhinus canicula*)		
brain	12	40
gill	13	176
gut	-	41
heart	-	274
liver	9	479
muscle	-	41
spleen	-	307
Bib (*Trisopterus luscus*)		
brain	-	-
gut	4	-
liver	0.3	143
muscle	-	187
skeletal tissue	-	185

TABLE 4-3. (continued)

Species	PCE	Trichloroethylene
	(mg x 10^6/g dry weight tissue)	
Baccinum undatum		
digestive gland	33	2
muscle	39	-
Modiolus modiolus		
digestive tissue	-	56
mantle	63	250
muscle	16	33
Pecten maximus		
gill	88	detected
mantle	40	-
muscle	24	-
ovary	-	-
testis	176	-

Source: Dickson and Riley, 1976.

4.3 BEHAVIOR IN WATER AND SOIL

The potential of any substance for bioconcentration is influenced by many factors, including the rate at which it volatizes and its reactivity.

In the laboratory study by Dilling et al. (1975), the measured half-life of PCE ranged from 24 to 28 minutes in water. Factors affecting the evaporation of PCE were surface wind speed, agitation of the water, and water and air temperatures. Reactivity of PCE in water was measured by exposing sealed quartz tubes containing 1 ppm PCE to sunlight for one year. At 6 months, the level of PCE had declined to 0.52 ppm, and at 1 year, to 0.25 ppm. Dilling et al. (1975) reported that the presence of 3 percent NaCl (as in seawater) caused about a 10 percent decrease in the evaporation after 40 percent had already evaporated. The addition of 500 ppm clay appeared to increase the rate of disappearance to 85 percent soluble depletion at 20 minutes. These experiments were conducted to simulate the evaporation of PCE under conditions more nearly like those found in the environment. Evaporation of PCE from the hydrosphere is a rapid process.

The field studies of Zoeteman et al. (1980) suggest that PCE is more persistent in natural water environments than is indicated by laboratory measurements. In a field study of the persistence of a variety of organic chemicals in different aquatic environments in the Netherlands, Zoeteman et al. (1980) estimated the persistence of PCE in river water from 3 to 30 days (half-life). In lakes and groundwaters, the half-life was estimated at 10-fold higher. Estimates were derived from monitored values of samples collected between two sites along the Rhine River, into which no discharges were expected. PCE was analyzed by GC-MS.

Estimates of the persistence of PCE in rivers, lakes, and ponds, by calculation according to Smith et al. (1980) are in general agreement with the field results of Zoeteman and coworkers (1980). The half-life of PCE is obtained from the expression:

$$t_{1/2} = \frac{0.693}{k_v^c}, \qquad (4\text{-}2)$$

where k_v^c is the volatilization rate constant.

Using the data provided by Smith et al. (1980), the $t_{1/2}$ (days) is as follows: ponds, 9 to 20; lakes, < 1 to 20; rivers, < 1 to 20.

Bouwer et al. (1981) found that PCE and other halogenated organics have the potential to leach rapidly through soil. When secondary treated municipal wastewater containing from 1 to 10 ng/l PCE was applied to soil columns, at rates typical of high-rate land application systems and under conditions in which volatilization was prevented, PCE was detected in the effluent. Leaching of PCE through soil was suggested by Zoeteman et al. (1980) as a probable factor in the contamination of groundwater supplies in the Netherlands.

The potential for halogenated organics, including PCE, to contaminate groundwater supplies via leaching from surface waters was examined by Scwarzenbach and Westall (1981). In batch and column experiments with various types of sorbents and organics designed to simulate field conditions, these investigators found that the partition coefficient for a particular compound can be estimated from its octanol/water partition coefficient and from the fraction of organic carbon in the sorbent. A high degree of correlation was found between the partition coefficient and organic carbon content when the fraction of organic carbon was greater than 0.1 percent. A partition coefficient of 0.56 ± 0.09 was found for PCE, using natural aquifer material (organic carbon = 0.15 percent) from a field site in Switzerland. It was concluded that, for concentrations typically encountered in natural waters, sorption of PCE and other organics of comparable lipophilicity by aquifer materials is reversible. The expression

$$S = kpC, \tag{4-3}$$

where S = concentration in solid phase
kp = partition coefficient
C = concentration in liquid phase

was found satisfactory to describe sorption equilibrium.

4.4 SUMMARY

The available data for PCE indicate that acute and chronic toxicity to freshwater aquatic life can occur at concentrations around 5280 and 840 µg/l, respectively. For saltwater aquatic life, the acute and chronic toxicity values are 10,200 and 450 µg/l, respectively.

Tetrachloroethylene does not appear to biomagnify or concentrate as it moves up the food chain. The available data suggest that the bioconcentration potential of PCE is low, and it appears to be eliminated rapidly from aquatic organisms.

Contamination of groundwater supplies by PCE leaching through soil could be a concern, particularly in situations in which soils of low organic carbon content are involved.

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5. COMPOUND DISTRIBUTION AND RELATED PHARMACOKINETICS

5.1 HUMAN AND ANIMAL STUDIES

5.1.1 Absorption

5.1.1.1 Pulmonary--Inhalation is the principal route by which tetrachloroethylene (PCE) enters the body. During inhalation, PCE is absorbed by the blood via alveolar air. The principal approaches used in calculating the amount absorbed are those involving serial breath analysis, i.e., measuring the amount exhaled.

The magnitude of PCE uptake into the body (dose, burden) depends primarily on several parameters: inspired air concentration, pulmonary ventilation, duration of exposure, and the rates of diffusion into and solubility in blood and the various tissues. The concentration of PCE in alveolar air, in equilibrium with pulmonary venous blood, approaches a minimum difference with the concentration in the inspiratory air until a steady-state condition is reached. After tissue and total body equilibrium is reached during exposure, uptake is balanced by elimination through the lungs and by other routes, including metabolism. The difference between alveolar and inspiratory air concentrations, together with the ventilation rate (about 6 l/min at rest), provides a means of calculating uptake during exposure:

$$Q = (C_{ins} - C_{alv})\,\dot{V} \cdot T \qquad (5\text{-}1)$$

where Q is the quantity absorbed; C is the air concentration in milligrams per liter; $\dot{V}$ is the alveolar ventilation rate in liters per minute; and T is the duration of exposure in minutes. The percent retention is defined as $(C_{ins} - C_{alv})/C_{ins} \times 100$, and percent retention x quantity inspired $(\dot{V} \cdot T \cdot C_{ins})$ is equal to uptake.

In serial determinations of PCE in alveolar breath and in blood, during and following exposure (1, 3, 5.5, and 7.5 hr/day) of males and females to 25, 50, 100, and 150 ppm (170, 339, 678, and 1017 mg/m^3), Hake et al. (1976) concluded that the compound was rapidly absorbed and rapidly excreted via the lungs. The amount absorbed at a given vapor concentration was reported to be related to the respiratory minute volume. The minute volume is defined as the product of the tidal volume and the respiratory frequency over a 1-minute period.

In a study by Monster et al. (1979), six male volunteers were exposed in a chamber for 4 hours to 72 ± 2 ppm PCE (488 ± 13 mg/m^3) and to 144 ± 7 ppm PCE (977 ± 47 mg/m^3) while at rest. Absorption of PCE by the lungs was reported to decrease with continuation of exposure ($p < 0.05$); approximately 25 percent less PCE was absorbed in the fourth hour as compared with the first hour of exposure. The effects of a workload (bicycle ergometer) were determined in a separate exposure of the volunteers to 142 ± 6 ppm PCE (963 ± 41 mg/m^3); individuals exercised for two 30-minute periods during the 4-hour exposure period. A 2-week interval occurred between each exposure mode. During each mode, the individuals inhaled vapors through a gas mask and exhalations were made into a Tedlar® bag.

The total uptake, shown in Table 5-1, was influenced more by lean body mass than by respiratory minute volume or adipose tissue. Uptake is defined as the amount of PCE absorbed per minute. The inter-individual coefficient of variation of body burden predicted by measurements of PCE in exhaled air or in blood was about 25 percent. The individual uptake at 144 ppm PCE (977 mg/m^3) was 2.1 times higher than that at 72 ppm (488 mg/m^3) when individuals were at rest. During exercise, total uptake increased about 40 percent; exercise had no effect on the half-life of elimination or on the rate constant of elimination. Minute volume was three-fold higher than that observed when the individuals were at rest. An alveolar retention of approximately 60 percent was calculated at the end of the 4-hour exposure period. Alveolar retention is defined as the percentage difference between the amount of PCE inhaled and the amount exhaled.

Monster (1979) suggested that the decrease in absorption (declining lung clearance) as exposure continued reflected the small degree to which PCE was metabolized, in contrast to trichloroethylene, which has a more constant rate of absorption but is metabolized to a much greater degree. There would be no reason to expect that chronic exposure to environmental levels of PCE would not follow the patterns of absorption and lung clearance observed by Monster and coworkers. In the linear pharmacokinetic range, these parameters would remain proportional to the exposure concentration down the dose-response curve.

5.1.1.2 Percutaneous--Under most circumstances of use, absorption of PCE through the skin is of minor consideration. Stewart and Dodd (1964) observed absorption in each of five individuals after one thumb of each was immersed in

TABLE 5-1. ESTIMATED UPTAKE OF SIX INDIVIDUALS EXPOSED TO TETRACHLOROETHYLENE WHILE AT REST AND AFTER REST/EXERCISE

	Uptake, according to TCE exposure concentration					
Subject	72 ppm (at rest)	144 ppm (at rest)	142 ppm (rest and exercise)	Body mass, kg	Lean body mass, kg	Minute volume at rest, l/min
A	370	670	1060	70	62	7.6
B	490	940	1500	82	71	11.6
C	530	1000	1400	82	71	10.0
D	500	1210	1510	86	74	11.3
E	390	880	1320	67	61	12.3
F	450	970	1120	77	61	8.8

Source: Monster, 1979.

a beaker of PCE, which was located in a ventilated hood. By measuring concentrations in alveolar breath samples, the investigators concluded that there is little likelihood that toxic amounts of PCE will be absorbed through the skin during normal use or exposure to the compound.

Riihimäki and Pfäffli (1978) concluded that PCE concentrations found in the work environment were not likely to result in a significant amount of PCE being absorbed through the skin. In their experiment, three individuals who wore full facepiece respirators to prevent pulmonary absorption and were dressed in thin cotton pajamas and socks were exposed to 600 ppm PCE (4069 mg/m^3) for 3.5 hours. During each midhour, for a period of 10 minutes, each person exercised on a bicycle ergometer. The periodic exercise was employed to simulate work conditions. Tidal and alveolar air (mixed) were collected in polyester-lined polyethylene bags. Concentrations of PCE in blood and in exhaled air were determined up to 20 and 50 hours, respectively. The amount absorbed (assuming 98 percent is exhaled) was calculated at 7 ppm PCE (47.6 mg/m^3).

Jakobsen et al. (1982) found that PCE was absorbed through the skin of anesthetized guinea pigs after epicutaneous exposure. A maximum blood concentration was observed after 1 hour, followed by a rapid decrease during the rest of the exposure time. PCE was applied to a clipped area of the skin and sealed under a glass ring.

Kronevi et al. (1981) found that PCE, when applied to the skin of guinea pigs, caused considerable local skin changes within 15 minutes of topical exposure. Jakobson et al. (1982) suggested that these skin changes might reflect a defense reaction against penetrating agents.

5.1.2 Distribution

Tetrachloroethylene is believed to partition in body tissues having a high lipid content (Stewart, 1969). This site probably accounts for the prolonged retention of PCE. Such retention in adipose tissue is suggested by the blood/air and fat/blood partition coefficients of 16 and 90, respectively (Monster, 1979). However, the time needed to saturate adipose tissue to 50 percent of its equilibrium concentration is high, about 25 hours.

In an abstract, Hake et al. (1976) reported that "the solvent was rapidly absorbed and excreted via the lungs with a small portion accumulating in the body which was slowly excreted." Male and female volunteers were exposed for 1.3, 5.5, and 7.5 hr/day to 25, 50, 100, and 150 ppm PCE (170, 339, 678, and 1017 mg/m^3).

Because of selective partitioning of PCE in adipose tissue, a long period (about 2 weeks) is necessary to eliminate PCE from the body completely upon cessation of exposure (Monster et al., 1979; Fernandez et al., 1976). Uptake of PCE by adipose tissue will take place during repeated exposures until an equilibrium is reached; further exposure will not result in further accumulation (Schumann et al., 1980).

Guberan and Fernandez (1974) used a mathematical model to calculate uptake and distribution of PCE in the body, and they predicted that fatty tissues would show the slowest rate of PCE depletion because of the high solubility of PCE in fatty tissues. Serial breath concentration decay data obtained from 25 volunteers exposed to between 50 and 150 ppm PCE (339 and 1017 mg/m^3) for up to 8 hours were used in developing the model. As shown in Figure 5-1, theoretical curves of concentration in alveolar air (C_{alv}) divided by the concentration in inspired air (C_{ins}) versus exposure time for various post-exposure times can be used to estimate unknown concentrations to which an individual may be exposed.

Savolainen et al. (1977) found that exposure of two strains of rats to 200 ppm PCE (13,560 mg/m^3) for 6 hr/day for 4 days resulted in partitioning of

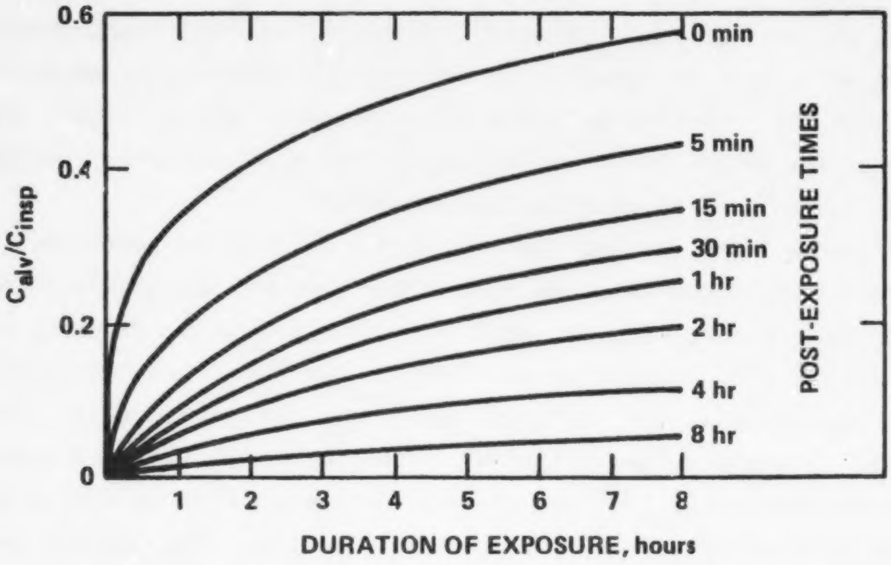


Figure 5-1. Predicted post-exposure alveolar air concentrations of tetrachloroethylene at various times against duration of exposure.

Source: Guberan and Fernandez, 1974.

PCE in perirenal fat, brain, and liver. Statistical analyses were not performed. When behavioral patterns were observed subsequent to the last exposure, ambulation frequency of exposed rats increased ($p < 0.05$) compared to controls. Rearing frequency, defecation and urination frequency, and preening frequency were not affected by exposure.

5.1.3 Metabolism (Animal Studies)

The hepatotoxic, carcinogenic, and mutagenic potentials of a number of chlorinated ethylene compounds (U.S. Department of Health, Education, and Welfare, 1977a,b,c; Viola et al., 1971; Maltoni and Lefemine, 1974; Creech and Johnson, 1974; Waxweiler et al., 1976) have generated considerable interest in the metabolic pathways of these compounds. Certain relatively inert chemicals may be activated by biotransformation to carcinogenic intermediate metabolites that could have the potential to induce a carcinogenic lesion. Thus, the relationship of the metabolism of the various chlorinated ethylenes, including PCE, to their toxicity is an important consideration.

The cytochrome P-450 dependent mixed-function oxidases of mammalian liver microsomes have been demonstrated to oxidize the carbon-carbon double bond in olefins to an epoxide ring (Liebman and Ortiz, 1968; Watabe and Maynert, 1968; Liebman and Ortiz, 1970; Maynert et al., 1970). The stability of the epoxide ring varies, depending on the configurations of the oxirane compound. Thus, this activated intermediate metabolite may interact covalently with a variety of cellular macromolecules. If the chemical interacts with nucleic acids and/or proteins that are essential to cellular function, the reaction may result in alteration of cellular metabolism, resulting in cellular necrosis, or in carcinogenic or mutagenic lesions (Jerina and Daly, 1974).

The formation of an epoxide intermediate for a chloroethylene compound was originally postulated by Powell in 1945. Later, Yllner (1961) and Daniel (1963) speculated that PCE might be oxidized to an epoxide as an intermediate metabolite during its biotransformation. Recent interest in this hypothesis has resulted from findings that vinyl chloride is carcinogenic in man and animals (Viola et al., 1971; Creech and Johnson, 1974; Maltoni and Lefemine, 1974; Lee and Harry, 1974) and the observation that this carcinogenicity is probably caused by formation of an epoxide intermediate, chloroethylene oxide. This mechanism was proposed by van Duuren in 1975. Tetrachloroethylene epoxide, as well as other chloroethylene epoxides, have been synthesized *in vitro*

(Kline et al., 1978; Kline and van Duuren, 1977; and Derkosch, 1976). These epoxides are unstable (have short half-lives) and are highly reactive.

Yllner (1961) studied the metabolism of ^{14}C-labeled PCE in mice exposed for 2 hours by inhalation to doses of 1.3 mg/g. Seventy percent of the absorbed radioactivity was expired in air, 20 percent was excreted in the urine, and less than 0.5 percent was eliminated in the feces. Of the total amount of radioactivity excreted in the urine, 52 percent was identified as trichloroacetic acid, 11 percent as oxalic acid, and a trace was dichloroacetic acid. No radiolabeled monochloroacetic acid, formic acid, or trichloroethanol was detected. Of the remaining radioactivity in the urine, 18 percent was not extractable with ether, even after hydrolysis.

Daniel (1963) fed ^{14}C-labeled PCE to rats and found that excretion was largely of unchanged compound through the lungs (half-time of expiration was 8 hours). Only 2 percent of the radioactivity was excreted in the urine, and equimolar proportions of trichloroacetic acid and inorganic chloride were the only metabolites detected.

Other investigators (Ogata et al., 1971; Ikeda and Ohtsuji, 1972; Ikeda, 1977; Moslen et al., 1977; Dmitrieva, 1967; Tada and Nakaaki, 1970; Boillat, 1970; Barchet et al., 1972) have reported that trichloroacetic acid (TCA) is a urinary metabolite of PCE in experimental animals and humans.

The most likely pathway for such product formation would be via epoxidation of the double bond. The resulting chloro-oxirane compound is known to be unstable and rearranges spontaneously. However, the stability of symmetric oxiranes such as the one formed from PCE is greater than that of the asymmetric oxiranes such as those formed from vinyl chloride, vinylidene chloride, and trichloroethylene. Henschler and his colleagues (Bonse et al., 1975; Greim et al., 1975; Henschler et al., 1975; Bonse and Henschler, 1976) have studied the chemical reactivity, metabolism, and mutagenicity of the chlorinated ethylene series, including vinyl chloride, trichloroethylene, and tetrachloroethylene. These investigators have reported a correlation between biological activity and chemical structure: those chlorinated ethylenes that are symmetrical, such as cis- and trans-1,2-dichloroethylene and PCE, are relatively stable and not mutagenic. In contrast, the asymmetrical ethylenes, vinyl chloride, vinylidene chloride, and trichloroethylene, are unstable and mutagenic. Although these investigators recognized that oxiranes (epoxides) may be formed by all six of the chlorinated ethylenes, they concluded that the asymmetrical oxiranes are far less stable than the symmetrical ones, and therefore are more highly electrophilic and may react directly with nucleophilic constituents of cells more readily, thereby exerting mutagenic or carcinogenic effects. The results of the mutagenic tests conducted by these investigators correlate with this structure-activity relationship.

Evidence for the involvement of the microsomal mixed-function oxidase system in the metabolism of PCE was shown by Moslen et al. (1977). Rats that were pretreated with phenobarbital or Arochlor-1254 (polychlorinated biphenyls), which are inducers of the hepatic mixed-function oxidase system, showed a significant increase in total trichlorinated urinary metabolites and TCA excretion following a single oral administration of 0.75 ml/kg PCE. Hepatotoxicity of PCE was enhanced by Arochlor-1254 pretreatment, as evidenced by doubling of serum glutamic-oxaloacetic transaminase (SGOT) levels, and by the appearance of focal areas of vacuolar degeneration and necrosis of the liver. However, Cornish et al. (1973) did not observe a potentiation of PCE toxicity following intraperitoneal injection of 0.3 to 2.0 ml/kg PCE to rats pretreated with phenobarbital. (The LD_{50} for the mouse is 2.9 ml/kg [Klaasen and Plaa, 1966]). However, elevation of SGOT was noted at all dose levels in this study.

Costa and Ivanetich's recent *in vitro* studies (1980) concerning the extent of metabolism of PCE provide further evidence of the central role of hepatic microsomal cytochrome P-450 in the metabolism of PCE. Two distinct forms of P-450, one induced *in vivo* in rats by phenobarbital and the other induced by pregnenolone-16α-carbonitrile, were shown to be active in the *in vitro* binding and metabolism of PCE. P-448, induced by B-napthoflavone, was not active in the *in vitro* system.

Spectral binding of PCE to P-450 in microsomes was measured by the difference in absorbance between 386 nm and 418 nm. Metabolism was estimated *in vitro* by the maximal rate of production (V_{max}) of TCA per minute per nmole of P-450. The spectral binding constant (K_s) associated with P-450 from uninduced rats was 0.4 mM. Phenobarbital-induced P-450 had no effect on K_s, but P-450 from pregnenolone-16α-carbonitrile-induced rats increased K_s.

V_{max} was significantly increased ($P < 0.01$) increased above controls (uninduced rats) when the microsomal preparation was derived from either of the inducers. Phenobarbital induction resulted in a lowering of the Michaelis-Menton (K_m) constant, indicating an increased affinity for the associated enzymes. The K_m was increased when the microsomes were derived from pregnenolone-16α-carbonitrile induction. The P-448 inducer, β-napthoflavone, had no effect on any of these parameters.

The rate of carbon monoxide-inhibitable NADPH oxidation by PCE was elevated significantly ($P < 0.01$) above noninduced controls by phenobarbital-induced microsomes. Induction by pregnenolone-16α-carbonitrile was without effect in this system. Metyrapone, a specific inhibitor of P-450, reduced spectral binding, NADPH oxidation, and metabolism by PCE 80, 65, and 75 percent, respectively. SKF-525A reduced spectral binding and metabolism 19 and 33 percent, respectively. The microsomal preparation used in the system was derived from phenobarbital-treated rats. The major metabolite in the _in vitro_ system was observed to be unbound TCA. Trichloroethanol was not found in appreciable amounts. Levels of P-450, as well as cytochrome b_5, heme, NADPH-cytochrome reductase, and glucose-6-phosphatase, were not reported to be altered, whether the inducer was phenobarbital or pregnenolone-16α-carbonitrile.

Kaemmerer et al. (1982) reported that feeding rats 25 ppm PCE in feed resulted in a statistically significant induction of cytochrome P-450 in rat liver homogenates 14 days after administration, compared to untreated controls. When 500 ppm was used, the increase occurred after 7 days. The authors also reported that blood coagulation was impaired in rats. The authors concluded that PCE interferes with basic physiologic functions, particularly cell metabolism.

Takano and Miyazaki (1982) reported that the PCE inhibited glutamate, succinate, and malate oxidation in the presence of rat liver mitochondria. The lesser inhibition of succinate oxidation suggested to the authors that PCE may act as an uncoupler in the electron transport process between NADH and coenzyme Q. Ogata and Hasegawa (1981) have reported similar findings for PCE and other halocarbons in succinate oxidation by rat liver mitochondria.

The extent of metabolism of PCE and its binding to hepatic macromolecules in mice (B6C3F1) and rats (Sprague-Dawley) was investigated by Schumann et al. (1980). Animals were exposed for 6 hours via inhalation to 10 and 600 ppm ^{14}C-labeled PCE (67.8 and 4068 mg/m^3). Purity was determined to be greater than 98 percent. Following inhalation of 10 ppm (67.8 mg/m^3) ^{14}C-labeled PCE by mice, urinary metabolites were observed to account for 62.5 percent of the total radioactivity recovered, though unchanged PCE in expired air accounted for only 12.0 ±1.3 percent. The reverse situation was observed after a single oral dose of 500 mg ^{14}C-labeled PCE/kg body weight: 82.6 percent of the total recovered radioactivity was in the form of unchanged PCE in expired air in the mouse. This shift in the mouse in the major route of elimination demonstrates a saturation of oxidative metabolism. Metabolites accounted for 10.3 percent. When compared to the extent of metabolism in rats (Pegg et al., 1979), it was calculated that the mouse metabolized 8.5 and 1.6 times more PCE than rats at 10 ppm (67.8 mg/m^3) and 500 mg/kg, respectively.

Following exposure of rats and mice to 10 and 600 ppm ^{14}C-labeled PCE (67.8 and 4068 mg/m^3), no radioactivity was observed to be bound to purified hepatic DNA. The detection limit was 14.5 alkylations/10^6 nucleotides at the 600 ppm (4068 mg/m^3) level. Lack of binding to DNA also was observed following a single oral dose of 500 mg/kg ^{14}C-labeled PCE. However, at times of peak binding to hepatic macromolecules, 4.7-, 5.8-, and 4.4-fold more radioactivity was irreversibly bound in the mouse than in the rat following exposure to 10 or 600 ppm (67.8 or 4068 mg/m^3), or 500 mg/kg, respectively. The extent of hepatic macromolecular bindings was determined subsequent to homogenization of the liver. The authors noted that the 60-fold increase in exposure level resulted in a 10-fold increase in the extent of binding in both rats and mice. This result suggests that metabolism of PCE is a saturable process. Binding was determined at intervals up to 72 hours post-exposure. The lack of binding to DNA was suggested by the authors as evidence indicating that PCE lacks genotoxic potential. An absence of binding to DNA does not preclude such an event that occurs below the detection limit of alkylation. Effects of treatment on body weight and liver are reported in Chapter 6. A briefer discussion of the results of Schumann and coworkers was presented by Watanabe et al. (1980).

A low rate of metabolism (2.8 mmole/kg) of PCE was reported by Bolt et al. (1982) during exposure of newborn female Wistar rats for 10 weeks at 2000 ppm (13,560 mg/m^3). The reported metabolic rate was 7 μmole/hr/kg, a rate 30-fold less than that reported for trichloroethylene.

In the oral and inhalation exposure of male Sprague-Dawley rats, Pegg et al. (1979) found that by either route, PCE was eliminated in unchanged form, predominantly in expired air. In contradiction to evidence pertaining to humans and other species, Pegg and coworkers found oxalic acid to be the major urinary metabolite. TCA was not detected.

The protocol was similar to that used by Schumann et al. (1980) in exposures of mice and rats. Rats were exposed via inhalation (6 hours) to 10 and 600 ppm ^{14}C-labeled PCE (67.8 and 4068 mg/m^3). In the gavage experiment, 1 or 500 mg ^{14}C-labeled PCE/kg body weight was administered as a single dose.

After oral administration (500 mg/kg) or inhalation (600 ppm; 4068 mg/m^3), 89 percent of the radioactivity was recovered in expired air as PCE; 1 to 2 percent remained in the carcass. The difference was accounted for by ^{14}carbon dioxide (CO_2) and urinary and fecal metabolites. Pulmonary elimination was observed to be monophasic with a half-life of about 7 hours; it was independent of dose or route of administration. Radioactivity remaining in the carcass 72 hours after exposure by either route was primarily distributed in liver, kidney, and fat tissue. After oral administration of 1 mg/kg, only 72 percent of the radioactivity was recovered in expired air as PCE. Recovery of $^{14}CO_2$ and nonvolatile metabolites increased. The authors suggested that, in rats, metabolism of PCE is a saturable process.

In blood, PCE levels peaked 1 hour after oral administration. Disappearance followed apparent first-order kinetics for up to 36 hours after exposure, with a half-life of 6 hours and an elimination constant of 0.12/hr. After termination of exposure to 600 ppm (4068 mg/m^3), PCE levels in blood declined similarly with a half-life of 7 hours and an elimination constant of 0.10/hr.

Whole liver radioactivity and that associated irreversibly with tissue macromolecules was assayed 0, 6, 24, and 72 hours after termination of exposure to 10 or 600 ppm ^{14}C-labeled PCE (67.8 or 4068 mg/m^3) and 72 hours after oral administration. Whole-liver radioactivity in livers from inhalation-exposed animals decreased exponentially during the 72-hour collection period as a biphasic process. The ratio of bound to metabolized radioactivity 72 hours after oral or inhalation exposure was not significantly different between the high and the low dose.

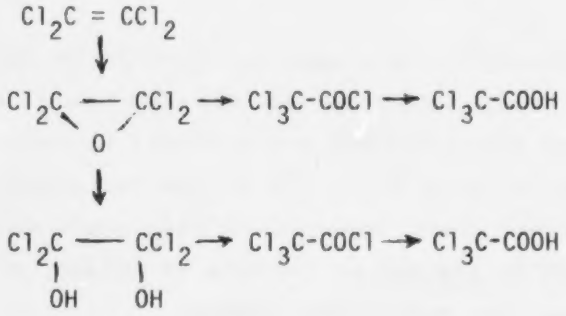
Nonprotein liver sulfhydryl levels were not found to be depleted, thus suggesting to Pegg et al. that glutathione was not involved in metabolism. The low rate of turnover of nonextractable radioactivity in liver macromolecules also suggested that accumulation of bound PCE metabolites could potentially occur upon repeated exposure. Such "accumulation" (or preferably, extent of binding) would be expected to plateau as the rate of uptake, elimination, metabolism, and protein turnover reached equilibrium.

Vainio et al. (1976) looked at the effects of PCE on liver metabolizing enzymes in vivo in the rat. Oral administration of 2.6 mmol/kg PCE was associated with a statistically significant lowering of concentrations of 3,4-benzpyrene hydroxylation and p-nitroanisole-o-methylation.

Plevova et al. (1975) showed that 6 hours of exposure to 177 ppm PCE (12,000 mg/m^3) 20 hours prior to administration of 44 mg/kg intraperitoneal pentobarbital sodium would lengthen pentobarbital sleeping time by 30 percent in Wistar rats. This effect was possibly mediated through hepatic drug metabolizing enzyme activity. Also, changes in spontaneous motor activity induced by intraperitoneal injection of pentobarbital, diazepam, amphetamine, and partly by chlorpromazine were enhanced by previous inhalation of PCE. This response probably resulted from an effect on metabolism rates.

Although TCA has been observed by several investigators to be a urinary metabolite of PCE, the excretion of total trichloro compounds, as measured by the nonspecific Fujiwara colorimetric reaction after oxidation, exceeded that of TCA. In some cases, this excretion was assumed to be trichloroethanol (Muenzer and Heder, 1972; Ikeda et al., 1972). In other studies, that portion that was not TCA could not be demonstrated to be trichloroethanol (Hake and Stewart, 1977). In one report, ethylene glycol was claimed to be a prominent metabolite in the rat (Moslen et al., 1977).

Leibman and Ortiz (1975, 1977) proposed a scheme (see below) for possible pathways of PCE metabolism. The formation of PCE epoxide by the hepatic mixed-function oxidase system may be followed by hydration of the epoxide to PCE glycol. Because of the symmetric arrangement of the epoxide and glycol intermediates, rearrangement of both would yield trichloroacetyl chloride, which hydrolyzes rapidly to TCA and, to a much lesser extent, TCE in the urine. Possibly, this response could be caused by dehydrohalogenation to oxalic acid, which has been reported by Pegg et al. (1979) and Yllner (1961).



Incubation of PCE and rat liver supernatant with a nicotinamide adenine dinucleotide phosphate (NADPH), reduced generating system confirmed the production of TCA. Nicotinamide adenine dinucleotide, reduced (NADH), did not promote the formation of TCA. Expoxide hydrase inhibition, produced by the addition of cyclohexane to the incubation mixture, did not have any effect upon TCA formation. Leibman and Ortiz (1977) concluded that, if the epoxide-diol pathway is operative, tetrachloroethylene oxide is not a substrate for hydration by epoxide hydrase, or that the epoxide and glycol rearrange to trichloroacetyl chloride at similar rates.

5.1.4 Excretion and Elimination

PCE is removed from the body in two principal ways: elimination as an unchanged compound in exhaled air and through elimination of its metabolites. During exhalation, the concentration of PCE in expired air is a function of a number of factors: (1) duration of exposure (until steady-state is reached) and the concentration in inhaled air, (2) rate of respiration, (3) time elapsed following exposure, and (4) total body lipid and other tissue repositories. The principal approach used to measure the amount and kinetics of elimination via the lungs is serial breath analysis of alveolar air.

From controlled exposure studies, Stewart and coworkers (Stewart, 1969; Hake et al., 1976; Stewart et al., 1970; Stewart et al., 1961a,b; Stewart et al., 1977; Stewart et al., 1974) concluded that PCE is rapidly excreted from the lungs and is principally excreted in unchanged form. These findings have recently been confirmed in the controlled exposure studies of Monster et al. (1979), who used serial breath analysis and found that between 80 and 100 percent of PCE is eliminated unchanged via the lungs.

The principal urinary metabolite of PCE is TCA, although trichloroethanol (TCE) has been reported by the nonspecific Fujiwara reaction to be a secondary metabolite. Other minor metabolites reported include oxalic acid, dichloroacetic acid, and ethylene glycol.

5.1.4.1 Controlled Studies--The concentration in alveolar air in the most immediate post-exposure period (up to 2 hours) is a reflection of the PCE concentration to which the individual was most recently exposed (Stewart et al., 1970; Stewart 1961b). The breath decay curves shown in Figure 5-2 were obtained from five males experimentally exposed to an average PCE concentration of 101 ppm (685 mg/m^3) for 7 hd/day on 5 consecutive days. The curves show that a high percentage of absorbed PCE was excreted during the 2-week period following exposure. A single 7-hour exposure of 15 volunteers to an average PCE concentration of 101 ppm (685 mg/m^3) resulted in a similar alveolar desaturation curve (Stewart et al., 1970). The range of concentrations from which the average was obtained was 62 to 137 ppm (420 to 929 mg/m^3). The increase of initial alveolar air concentration after repeated exposure (Figures 5-2 and 5-3) was suggested by the authors to be a result of the accumulation of PCE in the body tissues. However, as shown by Schumann et al. (1980), an equilibrium is rapidly reached where the body burden of PCE would not increase to a value greater than that of the previous day (Figure 5-2). The "hump" in the curve (Figure 5-3) is unexplained but was not considered by Stewart and co-workers to be artifactual. Breath samples, collected in glass pipettes and Saran bags, were analyzed by infrared spectroscopy.

After an exposure of six volunteers to approximately 100 and 200 ppm PCE (678 and 1356 mg/m^3), analyses of the breath decay curves indicated that (1) exposures of similar duration yielded decay curves with similar elimination rate constants, (2) the average concentration in the expired air was proportional to the vapor concentration for exposures of similar duration, and (3) the length of time that PCE could be measured in expired air was proportional to both the vapor concentration and the duration of exposure, i.e., it is proportional to the acquired body burden, which would plateau upon repeated exposure (Stewart et al., 1961a).

The concentration of PCE in the blood of those individuals exposed to 194 ppm (1316 mg/m^3) for 83 and 187 minutes approached a plateau near the end of the third hour of exposure. After exposure, PCE was rapidly cleared from the blood and was undetectable after 30 minutes.

Monster et al. (1979), in agreement with the general findings of Stewart and co-workers (Stewart, 1969; Hake et al., 1976; Stewart et al., 1970; Stewart et al., 1961a,b; Stewart et al., 1977; Stewart et al., 1974), found that 80 to 100 percent of the PCE absorbed was excreted unchanged; metabolism to urinary TCA accounted for less than 2 percent. Physical exercise resulted in increased uptake and an increase of PCE in blood levels; similar observations were made by Stewart et al. (1974).

In the study by Monster et al. (1979), discussed previously in Section 5.1.1.1, the concentration of PCE in exhaled air decreased when exposed individuals exercised. Recovery in exhaled air was 78 percent (exercise) as compared to 92 percent when the individuals were at rest. Exercise had no effect on the half-life of PCE elimination or on the rate constant of elimination. Minute volume and lung clearance were three-fold higher than the values obtained

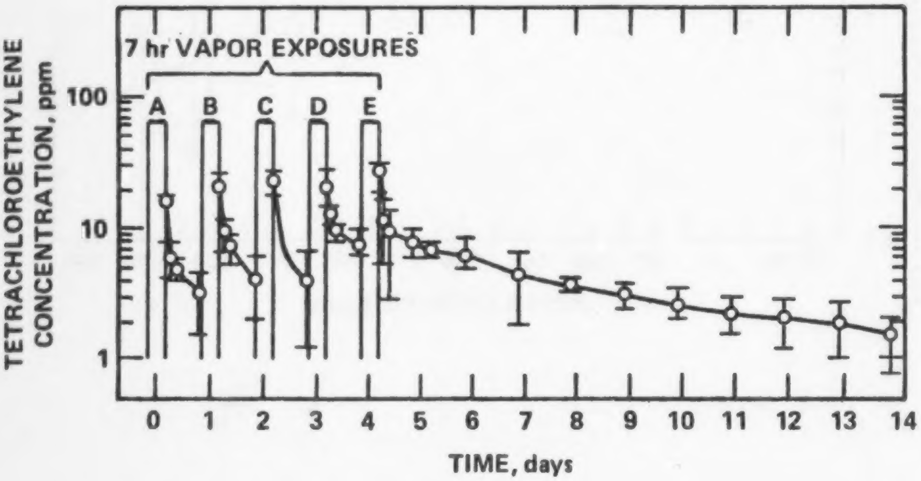


Figure 5-2. Mean and range of breath concentrations of tetrachloroethylene after exposure of individuals to single or repeated exposures.

Source: Stewart et al., 1970.

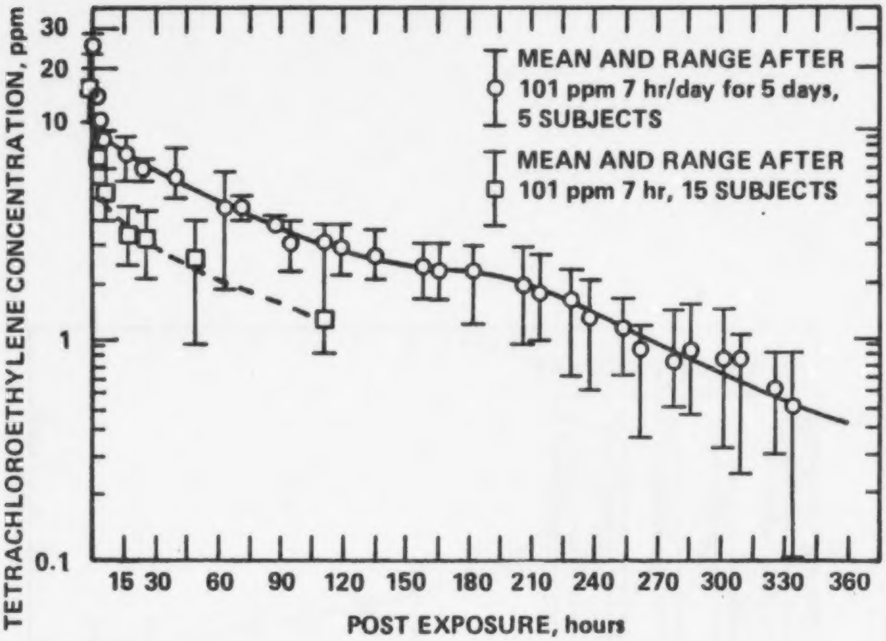


Figure 5-3. Mean and range of breath concentrations of five individuals during post-exposure after five separate exposures to 96, 109, 104, 98, and 99 ppm tetrachloroethylene.

Source: et al., 1970.

when the individuals were at rest. While exercise decreased the amount of PCE in exhaled air, uptake increased about 40 percent (Figure 5-1).

The concentrations of PCE in blood and in exhaled air during the post-exposure period are shown in Figure 5-4. Contrary to the finding of Stewart et al. (1961a) that blood concentrations of PCE were undetectable 30 minutes after exposure, Monster et al. (1979) found that the decrease of PCE in the blood paralleled the decay in expired air. The slopes of the curves in Figure 5-3 suggest that the half-lives of PCE in exhaled air and blood for three body compartments are for (1) tissues with high blood flow, (2) lean tissue, and (3) adipose tissue. The concentration of TCA (from metabolism) in the blood increased for 20 hours post-exposure before declining. Monster (1979) suggested that the increase in TCA concentration is smaller and that the maximum is reached earlier in contrast to exposures to trichloroethylene or methyl chloroform. The biological half-life of TCA in blood is the same for all solvents (about 80 to 100 hours). Upon repeated exposure to PCE, TCA would increase (Monster et al., 1979). However, TCA would be expected to eventually plateau and not increase beyond steady-state.

The time course of the PCE concentrations in blood and in expired air indicates that a long period (greater than 275 hours) is necessary to completely eliminate PCE from the body (Fernandez et al., 1976; Monster et al., 1979). Fernandez et al. (1976) found that 2 weeks were necessary to completely eliminate PCE from the body after exposure to 100 ppm (678 mg/m^3) for 8 hours. These findings agree with those of Monster et al. (1979). In these chamber studies, 24 volunteers were exposed for 1 to 8 hours to vapor containing 100, 150, and 200 ppm PCE (678, 1017, and 1356 mg/m^3). When the exposure time increased, the PCE concentration in alveolar air would plateau at steady-state.

Monster (1979) determined that the values for partition coefficients and lung clearance measurements between blood and vapor after exposure of four to six individuals to 70 to 140 ppm PCE (475 and 950 mg/m^3) for 4 hours indicated that (1) alveolar air concentration of PCE in the first few hours after exposure will be proportional to exposure concentration and to the concentration in blood and other rapidly exchangeable tissues, and (2) during that later phase of elimination, the alveolar air concentration will be proportional to the concentration in adipose tissue. As previously stated, the partition coefficient (37°C) for PCE between venous blood and alveolar air of 16 and the partition coefficient between fat and blood of 90 suggests that adipose tissue is a

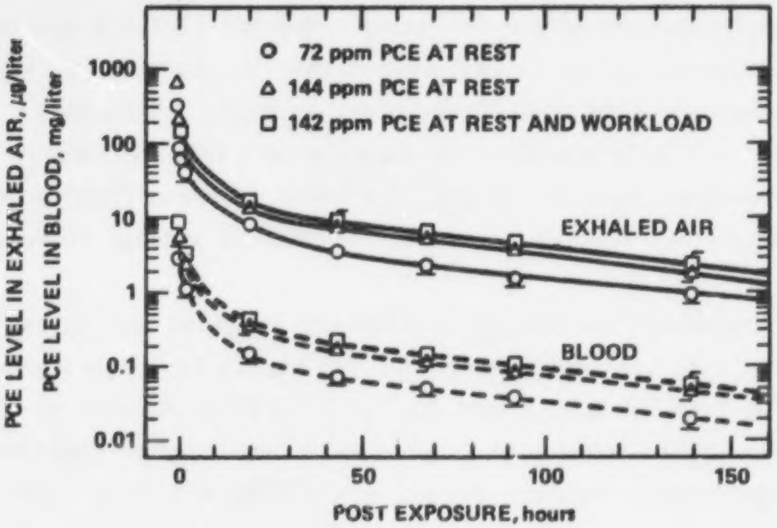


Figure 5-4. Tetrachloroethylene in blood and exhaled air following exposure to tetrachloroethylene for 4 hours. Each point represents the geometric mean ± standard deviation of six individuals.

Source: Monster et al., 1979.

primary storage site. Monster estimated that 25 hours would be necessary for PCE to saturate adipose tissue to 50 percent of its equilibrium concentration with plasma.

Metabolic considerations investigated in this study are discussed in Sections 5.1.3 and 5.1.4.

Evidence that blood levels of PCE may be useful in determining individual uptake was obtained in a single exposure to 70 and 140 ppm (475 and 950 mg/m^3) for 4 hours (Monster and Houtkooper, 1979). Concentrations of PCE in blood, urine, and exhaled air were determined at 2 and 20 hours after exposure. While a high degree of correlation was obtained between exhaled air concentration and blood concentration, linear and multiple linear regression analysis showed an inter-person coefficient of variation of 20 to 25 percent for blood measurements at 2 and 20 hours and in exhaled air at 2 hours.

Verberk and Scheffers (1980) suggest that measurements of PCE in expired air are useful in monitoring exposure in the general population as well as in populations of occupationally exposed people. PCE was measured in the expired air of residents living near 12 dry-cleaning shops. Residents were classified into two groups, corresponding to the distance they lived from the shops. In all cases, the residents living nearest the shop, the house next to the shop, had higher levels of PCE in expired air than residents who lived one house farther away from the shop.

In the study by Stewart and Dodd (1964), elimination of PCE via the lungs following percutaneous absorption was shown to be minor. Each of five individuals immersed one thumb in a beaker of PCE located in a ventilated hood. At intervals of 10 minutes, the concentration of PCE in exhaled air was measured. Before and periodically during each skin exposure, samples of breathing zone air were analyzed to preclude solvent vapor contamination. The mean peak breath concentration after a 40-minute immersion was 0.31 ppm (2.1 mg/m^3); 2 hours after exposure, the mean breath concentration was 0.23 ppm (1.6 mg/m^3). Five hours after exposure, PCE was still detectable (0.16 to 0.26 ppm; 1.1 to 1.8 mg/m^3).

The elimination of PCE through the skin was found by Bolańowska and Golacka (1972) to be approximately 0.02 percent per hour of the dose inhaled.

As previously mentioned, in both controlled and occupational exposures of humans to PCE, the principal urinary excretion product is TCA. Trichloroethanol has been reported by a nonspecific assay as a metabolite. TCE was indirectly measured by chromate oxidation of urine to TCA.

Hake and Stewart (1977) found only traces of TCA in 24-hour urine specimens from individuals exposed to 150 ppm PCE (1017 mg/m^3) and below. No TCE was detected.

Ogata et al. (1971) found TCA in the urine of four individuals exposed to 87 ppm PCE (590 mg/m^3) for 3 hours at a level of 1.8 percent of the total PCE dose. TCE could not be detected, but the urine contained 1 percent of an unidentified chlorine-containing compound. Urine was collected for 67 hours into the post-exposure period.

In the previously discussed studies of Monster and co-workers (Monster et al., 1979; Monster and Houtkooper, 1979), urinary TCA was found to represent less than 1 percent of the absorbed dose of PCE. In blood, TCA continued to increase until 20 hours post-exposure. From about 60 hours after exposure, the concentration decreased exponentially. A base level of 0.6 mg of TCA per day was found in the urine of subjects prior to exposure. Results of blood and urine concentrations are shown in Figures 5-5 and 5-6. The ratio of TCA_{urine} to TCA_{blood} was three-fold higher in the period 0 to 22 hours after the start of the exposure. The relatively high concentration in urine possibly was caused by an unknown compound measured by the non-specific Fujiwara reaction; TCA in blood was measured by gas chromatography. The unknown compound was not PCE or TCE.

Exposure combined with exercise resulted in 20 percent higher levels of excreted TCA, while uptake of PCE increased 40 percent. The TCA concentration at 20 hours after exposure was 1.6 times the concentration at the end of exposure. Inferences drawn from these results regarding metabolism of PCE are discussed in Section 5.1.3. Monster and Houtkooper (1979) concluded that TCA is not a reliable indicator of exposure to PCE.

5.1.4.2 Occupational Studies--In a study involving six dry-cleaning-plant workers exposed to PCE, an increase in urinary TCA was observed over the 50-hour sampling period (National Institute of Occupational Safety and Health, 1974). A control group not exposed to significant quantities of PCE also evidenced a similar increase. The average length of exposure for these individuals was 17 months. The worker evidencing the highest level of TCA in the urine had been exposed to an 8-hour time-weighted average of 168 to 171 ppm PCE (1139 to 1160 mg/m^3).

TCA and TCE (specific detection method not discussed) were found in the urine of 40 workers exposed to PCE concentrations ranging from 58 to 134 ppm

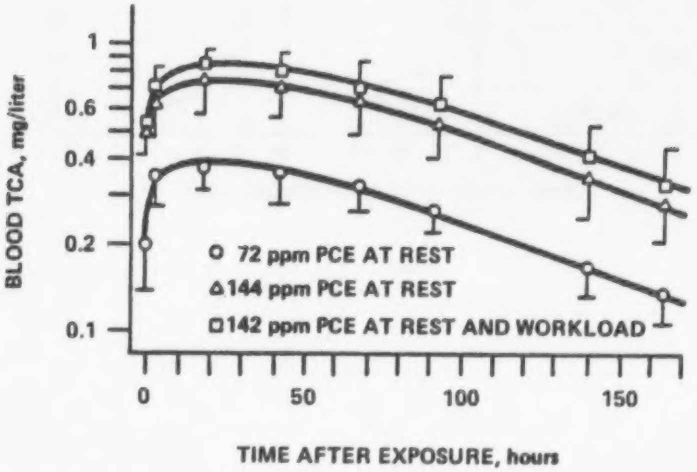


Figure 5-5. Trichloroacetic acid in blood following exposure to tetrachloroethylene for 4 hours. Each point represents the geometric mean ± the standard deviation of six subjects.

Source: Monster et al., 1979).

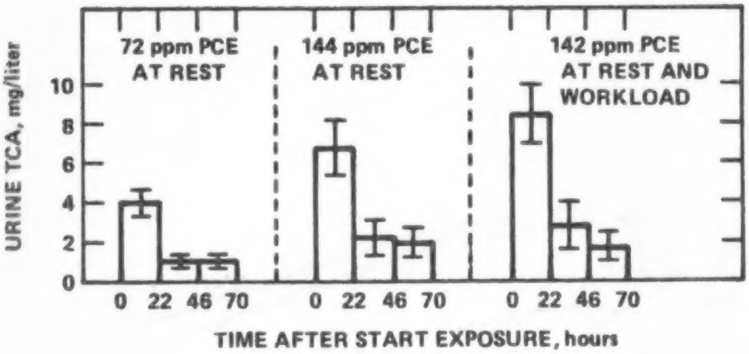


Figure 5-6. Urinary excretion of trichloroacetic acid following exposure to tetrachloroethylene for 4 hours. Each point represents the geometric mean ± the standard deviation of six subjects.

Source: Monster et al., 1979.

(393 to 909 mg/m^3) (Medek and Kovarik, 1973). The maximum levels observed were 41 mg TCA and 116 mg TCE per liter of urine. Seventy-two percent of these workers reported subjective complaints. No relationship was proposed between specific complaints and specific exposures or TCA and TCE levels. Exposed groups were not compared with blind controls.

Muenzer and Heder (1972) reported that urinary TCA was found in 124 of 200 dry-cleaning-plant employees. Seventy-one individuals had more than 10 mg/l. Liver function tests for exposed and unexposed (control) groups were comparable. The general room air in the work places contained between 200 to 300 ppm PCE (1357 to 2035 mg/m^3). An association between workroom air concentrations and TCA levels was not made.

Ikeda et al. (1972) reported evidence that TCA and TCE concentrations in the urine increased in proportion to environmental concentrations of PCE up to 50 ppm (339 mg/m^3). In this study, urine samples were collected from 34 male industrial workers who had been exposed to PCE vapors for 8 h/day for 6 days per week. Concentrations of PCE in the work place ranged from 10 to 400 ppm (68 to 2713 mg/m^3). The plateau observed in the urinary excretion curve for TCA suggested to the investigators that the capacity of humans to metabolize PCE is limited. The maximum level of TCA observed was approximately 50 mg/l of urine. For TCE, the maximum concentration reported was approximately 25 mg/l. TCE was measured indirectly by oxidation of urine with chromic oxide.

In another study, Ikeda and Ohtsuji (1972) reported a wide variation in the TCA and TCE levels in urine from occupationally exposed workers. One group of four workers had been exposed to a concentration range of 20 to 70 ppm (136 to 475 mg/m^3), while 66 workers in another group had been exposed to between 200 and 400 ppm (1357 and 2713 mg/m^3). The urine from the smaller group contained between 4 and 35 mg TCA and 4 to 20 mg of TCE per liter of urine. In the larger group, TCA levels were 32 to 97 mg/l and TCE levels ranged from 21 to 100 mg/l.

In their most recent study, Ohtsuji et al. (1983) obtained additional evidence that confirms reports by others that PCE is metabolized to a limited extent (approximately 2 percent) in humans. Personal monitoring of exposure, using carbon felt dosimeters, was carried out in two groups of workers (36 males and 25 females). Comparison of urinary total trichlorocompounds (expressed as TCA) with occupational levels of PCE suggested that metabolic capacity becomes saturated at about 100 ppm (678 mg/m^3) in air. Metabolite levels increased in a quasi-linear fashion up to 100 ppm PCE (678 mg/m^3)

High levels of TCA (greater than 60 mg/l of urine) also were reported by Weiss (1969) and by Haag (1958) in studies of individuals exposed occupationally.

5.1.4.3 Population Studies--Preliminary results reported by Ziglio (1981) suggest that plasma TCA can be a reliable indicator of the extent of chronic exposure to PCE. Ziglio chose 24 individuals in Milan, a city in which both trichloroethylene and PCE were present in tap water at concentrations as high as 150 to 200 μg/l (Giovanardi, 1979). Subjects were divided into two groups: exposed (those who drank water with halocarbon levels $\geq$ 50 μg/l) and nonexposed (those who drank water with levels $\leq$ 1 μg/l). When exposure increased, plasma TCA levels increased. However, the TCA levels were suggested by Ziglio to be more indicative of the extent of exposure to trichloroethylene, because this halocarbon is metabolized to a much greater extent than is PCE.

5.1.5 Estimates of Biological Half-life

Monster et al. (1979) determined from the concentration curves of PCE in blood and exhaled air after exposure (Figure 5-4) that PCE was eliminated from the body at three different rate constants with corresponding half-lives of 12 to 16, 30 to 40, and 55 hours, respectively; this result suggested that there are three major body compartments for PCE. The half-life, derived from the data of Stewart et al. (1970), was calculated to be 65 hours. The long half-life does not pertain to the major portion of the exposure but to a small percentage of the body burden (Hake et al., 1976). TCA in blood was reported by Monster et al. (1979) to have a predominant half-life (60 hours after exposure) of 75 to 80 hours.

Ikeda (1977) and Ikeda and Imamura (1973) reported that the mean biological half-life for PCE urinary metabolites is 144 hours. A possible sex difference, indicated from exposures of nine males and four females, has not been confirmed. The estimated biological half-life of PCE stored in adipose tissue is 71.5 hours (Guberan and Fernandez, 1974).

5.1.6 Interaction of PCE with Other Compounds

Stewart et al. (1976) conducted a study designed to determine the effects of alcohol and diazepam (Valium®) on 12 individuals exposed to 25 and 100 ppm PCE (170 and 678 mg/m^3) for 5.5 hours. Administration of alcohol to individuals during exposure to 25 ppm (170 mg/m^3) significantly increased blood levels of

PCE ($p < 0.01$), but there was no effect during exposure at 100 ppm (678 mg/m^3). Diazepam and alcohol each raised breath levels of PCE during exposure at 25 ppm (170 mg/m^3) but not at 100 ppm (678 mg/m^3). Results are shown in Table 5-2. Neither diazepam nor alcohol changed the effects of PCE as measured by behavioral and neurological tests.

5.1.7 Summary

Inhalation is the predominant route of exposure for humans, although contamination of potable water supplies indicates that oral ingestion represents an additional route of exposure. Percutaneous absorption is of minor consideration. In all species tested, PCE is rapidly absorbed and distributed to major body compartments. Because of its high octanol/water and fat/blood partition coefficients, PCE can be expected to selectively partition into lipid-rich tissues until an equilibrium is reached between uptake and elimination, after which additional accumulation would not occur. While most of the PCE is rapidly excreted, up to 2 weeks or more may be required to completely eliminate PCE from the human body (Fernandez et al., 1976). The estimated biological half-life of PCE in adipose tissue is about 70 hours. PCE would also be expected to partition into lungs, liver, kidney, spleen, and lean muscle until equilibrium is reached. The rate of tissue loading in humans, with a given inspired air concentration, is increased with physical activity and with exposure duration.

PCE is postulated to be metabolized via oxidation by the cytochrome P-450 mixed-function oxidase system. An epoxide intermediate, formed during metabolism, is believed to represent a species capable of binding covalently to tissue macromolecules. In vitro experiments (Costa and Ivanetich, 1980) have shown that a cytochrome P-450 activation system from rats binds and metabolizes PCE; TCA was identified as the principal reaction product. The in vivo studies by Pegg et al. (1979) in rats and by Schumann et al. (1980) in mice have demonstrated irreversible binding of PCE and/or its metabolites to hepatic macromolecules; binding to DNA, however, was not observed. Differences in metabolism of PCE in animals and humans, who have shown very little metabolism of PCE, seem to exist. In view of these metabolic differences between humans and rodents, little binding of PCE metabolites to human hepatic macromolecules would be expected.

Pegg et al. (1979) and Schumann et al. (1980) have suggested that the metabolism of PCE is a saturable, dose-dependent process and that the extent

TABLE 5-2. ALCOHOL AND DIAZEPAM EFFECTS UPON TETRACHLOROETHYLENE (PCE) BLOOD AND BREATH CONCENTRATIONS (5.5-HOUR EXPOSURES)

PCE in chamber, ppm	PCE in blood, ppm			PCE in breath, ppm					
	2 hours into exposure			2 hours into exposure			30 minutes post-exposure		
	PCE alone	PCE and alcohol[a]	PCE and diazepam[b]	PCE alone	PCE and alcohol[a]	PCE and diazepam[b]	PCE alone	PCE and alcohol[a]	PCE and diazepam[b]
25	1.65 (35)	2.92[c] (15)	1.76 (23)	11.03 (35)	12.35[d] (15)	11.72 (23)	6.40 (35)	7.40[c] (14)	6.96[d] (22)
100	8.25 (63)	7.95 (29)	8.47 (41)	33.2 (68)	32.3 (28)	35.5 (44)	17.62 (64)	13.83[c] (29)	17.35 (42)

[a] Alcohol blood levels of 30 to 100 mg percent.

[b] Diazepam blood levels of 7 to 30 mg percent.

[c] Significantly different from PCE alone at $p < 0.1$.

[d] Significantly different from PCE alone at $p < 0.05$.

Numbers in parentheses indicate the number of determinations.

Source: Stewart et al., 1977.

of reactive intermediate formation plateaus with increasing dose. This situation would explain why exposure to mice at 500 mg PCE/kg body weight would result in a carcinogenic response (see Chapter 9) in the National Cancer Institute bioassay but not an increase at a level of 1000 mg/kg.

Although TCA appears to be a predominant urinary metabolite in humans and rodents, metabolism in humans (in the form of urinary TCA) accounts for 2 percent or less of the absorbed dose. The estimated mean biological half-life for all PCE urinary metabolites in humans is 144 hours. Minor metabolites reported include TCE, oxalic acid, and ethylene glycol. However, Pegg et al. (1979) observed oxalic acid to be the principal urinary metabolite in rats. TCA was not detected upon incubation of a rat hepatic microsomal activation system with PCE. Costa and Ivanetich (1980) observed TCA to be the principal reaction product.

Elimination of PCE in expired air differs somewhat between humans, mice, and rats. Monster and coworkers (1979) have shown that humans may exhale as much as 98 percent of PCE in unchanged form. Exercise increases uptake (decreases pulmonary elimination) of PCE in the body. Repeated exposures to levels of 72 ppm (488 mg/m^3) or greater during sedentary conditions were observed to result in more PCE being eliminated unchanged in expired air; this situation is consistent with saturation of metabolism. At found or expected ambient air levels of exposure, the fate of PCE would not be altered regardless of exposure concentration in the linear pharmacokinetic range.

Elimination as the unchanged compound in expired air also is the predominant process in rats (Pegg et al., 1979), upon inhalation or oral exposure to PCE. However, in mice, urinary metabolites represent the chief elimination process at low exposures but not at high exposures (Schumann et al., 1980). Upon high oral dose exposure of mice, pulmonary elimination of unchanged PCE predominates (Schumann et al., 1980).

The dose level is a factor of particular importance when one considers the potential effects of PCE in humans. There appears to be no evidence that a different metabolite or a distinctively different pharmacokinetic pattern exists at high, as compared to low, exposure levels. Monster et al. (1979) has shown that a two-fold increase in exposure level resulted in a doubling of uptake; a shift in the nature of the urinary metabolites was not observed.

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6. TOXIC EFFECTS

6.1 HUMANS

The known effects of tetrachloroethylene (PCE) on humans have been established primarily from individuals accidentally or occupationally exposed to high (in some cases, unknown) concentrations of PCE. Exposure to high concentrations of PCE causes a variety of toxicological effects in humans. Effects upon the central nervous system (CNS) are generally the most noticeable following acute or excessive occupational exposures. Effects upon the liver and kidney usually are observed after an elapsed period of exposure to high concentrations.

6.1.1 Effects on the Liver

6.1.1.1 Acute Exposure Situations--Transient, mild hepatitis was diagnosed by Stewart (1969) in a worker occupationally exposed to high, anesthetic concentrations of PCE in a tank car for less than 30 minutes. Infrared analysis of the patient's exhaled breath 1.5 hours after exposure showed 105 ppm PCE (712 mg/m^3). Urinary urobilinogen levels were elevated on the ninth day of the post-exposure period. The serum glutamic-oxaloacetic transaminase (SGOT) level showed a slight increase on the third and fourth days. Stewart concluded this patient had experienced marked depression of the CNS followed by transient, minimal liver injury. The increase in urinary urobilinogen was suggested as one indicator of hepatic injury caused by PCE. Elevations in the levels of urobilinogen and other indicators of liver damage have been reported in other case studies involving acute exposures (Stewart et al., 1961a; Saland, 1967).

Stewart et al. (1961a) reported a case in which a male construction worker became semicomatose after being overexposed to fumes from a petroleum-based solvent, during a 3.5-hour period. The solvent was reported to contain 50 percent Stoddard Solvent and 50 percent PCE. A neurological examination conducted 1 hour after collapse indicated no abnormality of function; the liver was not palpable. During a 6-week period subsequent to the incident, neither clinical jaundice nor neurological symptoms were observed. Simulated exposure conditions suggested that the estimated average concentration of PCE in the work environment, during exposure, was 393 ppm (2666 mg/m^3). The average exposure for the first 3 hours was estimated to be 275 ppm (1864 mg/m^3).

The exposure for the remaining 30 minutes with the air hose turned off was 1100 ppm (7458 mg/m^3). Clinical tests revealed evidence of impaired liver function, beginning 9 days following exposure; urinary urobilinogen and total serum bilirubin were elevated. On the fourteenth post-exposure day, urinary urobilinogen was in the normal range, but a slight elevation of alkaline phosphatase was observed. Serum glutamine-pyruvic transaminase (SGPT) and SGOT values were in the normal range throughout the post-exposure period, with the exception that on the eighteenth day, SGPT was slightly elevated. On the sixteenth post-exposure day, the PCE concentration in expired air was sharply elevated. However, the overall decay curve slope was not altered appreciably. The investigators suggested that such an acute exposure may represent a continuing insult to the liver in view of the observations that PCE had an exceedingly long exponential decay in expired air, indicating slow release from body tissues. On the twenty-first day, no detectable PCE was found on the exposed worker's breath.

Elevated SGOT values and one enlarged liver were reported by Saland (1967). Nine firefighters were exposed to an unknown concentration of PCE upon responding to a complaint about fumes. All the firefighters were exposed without masks to unknown levels above the odor threshold for 3 minutes. No irritation of the eyes, mucous membranes, or respiratory tract occurred. For some inexplicable reason, all the firefighters were admitted to a hospital for study 12 days after the incident. All clinical tests indicated no abnormalities; however, eight of nine individuals had elevated SGOT levels. In seven individuals, SGOT values had returned to normal by 22 days after testing. Hepatomegaly and splenomegaly were found in one individual 12 days post-exposure. After 63 days post-exposure, the liver was not palpable.

An enlarged liver and obstructive jaundice were diagnosed by Bagnell and Ellenberger (1977) in a 6-week-old, breast-fed infant. While this situation is not uncommon in infants, the infant had been indirectly exposed to PCE. The child's father worked as a leather and suede cleaner in a dry-cleaning establishment where PCE vapors were present. During regular lunchtime visits to the exposure site, the mother had been exposed to the same vapors. These visits lasted between 30 and 60 minutes. The concentration of PCE in the work place was unknown, although it was believed to be excessively high because of reported episodes of dizziness. In the infant, bilirubin, SGOT, and serum alkaline phosphatase were elevated; other blood and urinary parameters of liver function were normal. Normal liver function was found in both parents. Analysis of the mother's blood 2 hours after one of her lunchtime visits indicated a PCE level of 0.3 mg per 100 ml. One hour after a visit, her breast milk contained 1.0 mg PCE per 100 ml. After 24 hours, the concentration of PCE in the breast milk decreased to 0.3 mg per 100 ml. Chlorinated hydrocarbons were not found in the mother's urine. One week after breast feeding was discontinued, serum bilirubin and serum alkaline phosphatase levels in the infant returned to a normal range. The findings suggest that the neonatal liver may be sensitive to toxicological effects of PCE, although other causal factors in this instance cannot be ruled out.

Levine et al. (1981) reported a diffuse and marked fatty metamorphosis of the liver of a 53-year-old male dry cleaner who succumbed to an overexposure of PCE over an unspecified period of time. During autopsy, the PCE concentration in the liver was 240 mg/kg. PCE was also detected in the blood (4.5 mg/l), brain (69 mg/kg), kidney (71 mg/kg), and liver (30 mg/kg). The authors noted that the liver was extremely fatty and that an ethanol concentration of 0.20 percent (w/v) was found in the blood.

Hake and Stewart (1977) reported mild liver injury, as indicated by elevated serum enzymes, in a 60-year-old male dry cleaning operator who was overcome by PCE vapors. The investigators estimated that the individual had been lying in a pool of solvent for about 12 hours. Although kidney and skin damage also were evident, the individual was released after 21 days of hospitalization and appeared fully recovered.

6.1.1.2 Chronic Exposure Situations--Hepatotoxic effects associated with persons working with unknown concentrations of PCE over extended periods have been reported by a number of investigators (Coler and Rossmiller, 1953; Franke and Eggeling, 1969; Hughes, 1954; Trense and Zimmerman, 1969; Meckler and Phelps, 1966; Larsen et al., 1977; Moeschlin, 1965; Dumortier et al., 1964). Liver function parameters that may be observed to be altered as a result of excessive PCE exposure include sulfobromophthalein retention time, thymol turbidity, serum bilirubin, serum protein patterns, cephalin-cholesterol flocculation, serum alkaline phosphatase, SGOT, and serum lactic acid dehydrogenase (LDH). However, these parameters may be observed as a result of many different causes that are completely dissociated with PCE.

Effects observed after exposure to PCE at high or unknown levels included cirrhosis of the liver (Coler and Rossmiller, 1953), toxic hepatitis (Hughes, 1954; Meckler and Phelps, 1966), liver cell necrosis (Trense and Zimmerman, 1969; Meckler and Phelps, 1966), and enlarged liver (Meckler and Phelps, 1966). In some cases, liver dysfunction parameters returned to normal following cessation of exposure (Hughes, 1954). In one case, the liver was enlarged 6 months after cessation of exposure (Meckler and Phelps, 1966).

Liver dysfunction was evidenced in a 24-year-old male who was admitted to the hospital with abdominal pains and blood-tinged vomitus (Larsen et al., 1977). Three days before hospitalization, this individual was exposed to PCE vapors emanating from recently dry-cleaned clothes. In this study, SGOT values increased four to five times above normal 1 day after initial symptoms. Two days later, SGOT returned to a normal range. The subject was found to have renal insufficiency and mild proteinuria. Despite diureses, serum creatinine and blood area increased constantly. Serum bilirubin was normal throughout hospitalization. Variations in the levels of SGOT and other liver function parameters during the post-exposure period indicate that repeated testing during this interval is required for complete diagnosis.

Larsen et al. (1977) also described an incident in which a female dry-cleaning worker was hospitalized in a comatose state with a grand mal seizure. Three days prior to hospitalization, she had worn clothing that had been recently dry-cleaned. Upon her admission, SGOT and serum LDH levels were reported to be strongly elevated; levels gradually decreased during hospitalization. Blood and protein were found in the urine. Elevated serum creatinine levels decreased after peritoneal dialysis. A cause-effect relationship is unproven.

Chmielewski et al. (1976) found that the activities of alanine and asparagine aminotransferase were significantly elevated ($t_{0.05} = 2.032$) in a group of 16 of 25 workers compared to non-exposed controls. This group of 16 workers had been exposed to PCE vapors in the range of 59 to 442 ppm (400 to 3000 mg/m^3) for periods ranging from 2 months to 27 years. Aminotransferase activity in a group of nine workers who were exposed to levels of PCE at or below 29 ppm (200 mg/m^3) was normal. These enzyme imbalances were indicative of liver cell injury by PCE. Low urinary excretion of 17-ketosteroids were observed in seven of nine persons whose exposures were less than 29 ppm and 4 of 16 persons whose exposures ranged from 59 to 442 ppm PCE. Abnormal electroencephalogram (EEG) tracings were reported in 10 persons. Six people were diagnosed as having a pseudo-neurotic syndrome, and in four other cases the researchers were led to diagnose or suspect encephalopathy.

6.1.2 Effects on Kidneys

Diminished excretion of urine (5 to 10 ml of urine per hour), uremia, and elevated serum creatinine was observed in a woman exposed to PCE vapors emanating from clothes that had been dry-cleaned (Larsen et al., 1977). As previously described, she had been admitted to the hospital in a comatose state with a grand mal seizure. During hospitalization, urine excretion and serum creatinine returned to normal. Renal biopsy suggested toxic nephropathy. Liver dysfunction also was evidenced by increased SGOT and bilirubin levels (Section 6.1.1). Protein and blood were detected in the urine. A cause-effect relationship was unproven.

In another situation in which an individual (male) had worn clothing permeated with PCE vapors, elevated serum creatinine and blood uremia were observed (Larsen et al., 1977). This individual was admitted to the hospital with abdominal pains and blood-tinged vomitus. Mild proteinuria and leukocytes and erythrocytes were found in the urine. Despite diuresis, serum creatinine and blood urea increased. Serum creatinine decreased with peritoneal dialysis, over a 19-day treatment period. Renal biopsy evidenced necrosis in the renal tubules.

Hake and Stewart (1977) reported renal damage, indicated by a proteinuria that lasted 20 days and hematuria lasting for 8 days, in a 60-year-old male dry-cleaning worker who was overcome by PCE vapors. Liver damage and skin damage also were reported. The individual was reported fully recovered upon release from the hospital (21 days post-exposure).

6.1.3 Effects on Other Organs/Tissues

6.1.3.1 Effects on the Pulmonary System--A 21-year-old male was found unconscious in a library, presumably from a massive but unknown concentration of PCE. After his admission to the hospital, the principal clinical feature was consistent with acute pulmonary edema (Patel et al., 1977). Bubbling rales were heard over the entire lung field. Recovery was complete 4 days after hospital admission. Liver and kidney function tests in this patient were normal.

Levine et al. (1981) reported pulmonary damage in a 53-year-old male drycleaner who succumbed upon overexposure to PCE vapors. Autopsy findings were congestion superimposed on mildly fibrotic and diffusely emphysematous lungs with apical bullous emphysema. The PCE concentration in lung tissue was

30 mg/kg. A co-worker, also overcome by vapors, was reported to have recovered without complications after hospitalization. The PCE concentration in the work place air at the time of the incident was not reported.

Alkaline phosphatase in leukocytes is a defense mechanism against bacterial infection, and it plays an active part in phagocytosis. In an investigation of the effects of PCE on alkaline phosphatase activity in human neutrophilic leukocytes, Friborska (1969) found that activity was within the normal range. In this study of occupational exposure, seven workers were exposed to PCE and four had been exposed to both PCE and trichloroethylene. For controls, 20 unexposed individuals were used. Trichloroethylene exposure, as opposed to PCE exposure, raised the activity of the alkaline phosphatase above the control level. For those individuals exposed to both compounds, no synergistic or additive effect was observed.

A slight depression in the total white blood cell count of three of nine firefighters exposed for 3 minutes to unknown concentrations of PCE was reported by Saland (1967). The white cell count was made 12 days after the firefighters were exposed to PCE.

6.1.3.2 Effects on the Skin--The effects of PCE upon the skin range from a mild to moderate burning sensation when direct contact occurs for 5 to 10 minutes, to a marked erythema after prolonged exposure, and finally, blistering if PCE is trapped under clothing or in shoes (Hake and Stewart, 1977).

Stewart and Dodd (1964) reported that individuals experienced a mild burning sensation on their thumbs after immersion of the thumbs in a solution of PCE for 5 to 10 minutes. After the thumbs were withdrawn, burning persisted without a decrease in intensity for 10 minutes before gradually subsiding after 1 hour. A marked erythema was present in all cases and subsided between 1 and 2 hours post-exposure.

Morgan (1969) reported erythema and blistering over 30 percent of the body of a worker who was anesthetized for 30 minutes after PCE overexposure in a coin-operated laundry.

Ling and Lindsay (1971) reported severe burns when an individual, upon losing consciousness, fell into a pool of PCE on the floor. The burns gradually healed within 3 weeks following exposure.

6.1.4 Behavioral and Neurological Effects

In nearly all the occupational situations involving short-term high-level exposures to PCE, an initial characteristic response is depression of the CNS.

Subchronic exposures to high levels produce characteristics of a neurasthenic syndrome; the most frequently reported subjective complaints are dizziness, headache, nausea, fatigue, and irritation of the eyes, nose, and throat. These symptoms are typical of many common ailments. Sensitivity may vary greatly among individuals.

6.1.4.1 Effects of Short-term Exposures--Stewart (1969) reported normal neurological findings, except for the Romberg test, in an individual who was found unconscious at the bottom of a tank car. Analysis of the man's breath 1.5 hours after exposure showed approximately 105 ppm PCE (712 mg/m^3). The Romberg test is designed to detect swaying motions when the subject stands with eyes closed. Upon return to work, the individual reported being very fatigued after 4 hours of light work. The individual's fatigue with slight exertion diminished over the 2 days following his return to work. Abnormal results of the Romberg test are suggested to be the earliest indications of signs of intoxication caused by PCE.

Rowe et al. (1952) reported that six individuals exposed to an average PCE concentration of 106 ppm (719 mg/m^3) (range = 83 to 130 ppm; 663 to 881 mg/m^3) did not evidence CNS effects. At an average PCE concentration of 216 ppm (1465 mg/m^3), all four individuals exposed for 45 minutes to 2 hours experienced slight eye irritation, which developed 20 to 30 minutes into the exposure period. Minimal, transient eye irritation led the authors to suggest that the vapor concentration causing this effect in unacclimatized individuals lies between 100 and 200 ppm (678 and 1356 mg/m^3). Dizziness and sleepiness also were noted. Recovery from all symptoms was complete within 1 hour after exposure. An exposure to an average concentration of 280 ppm PCE (1899 mg/m^3) for up to 2 hours resulted in complaints of lightheadedness, burning sensation in the eyes, congestion of frontal sinuses, and tightness about the mouth. Transient nausea was reported by one individual. The subjects felt that motor coordination was impaired and mental effort was required for coordination. Motor coordination was accomplished only with mental effort when two individuals were exposed to an average PCE concentration of 600 ppm (4070 mg/m^3). Recovery was complete within 1 hour after exposure. An average exposure concentration of 1060 ppm (7190 mg/m^3) for 1 minute was intolerable to three of four individuals. None experienced functional disturbances. Recovery was rapid.

No behavioral or neurological effects were reported by Carpenter (1937) when four individuals were exposed to 500 ppm (3391 mg/m^3) PCE for 70 minutes.

Short-term exposures to higher concentrations resulted in subject's reports of mental fogginess, lassitude, inebriation, loss of inhibition, and vertigo. At an exposure level of 1500 ppm (10,174 mg/m^3), shortness of breath, nausea, mental sluggishness, and difficulties in maintaining balance were reported during the post-exposure period. Tinnitus, ringing of the ears, was reported upon exposure to 2000 ppm PCE (13,565 mg/m^3) for 7.5 minutes.

Weichardt and Lindner (1975) recorded subjective responses of headaches, giddiness, numbness, alcohol intolerance, and intolerance of fats and fried foods as a result of exposures to between 11 to 45 ppm PCE (75 to 305 mg/m^3) for approximately 3 hours. Very little information about the work environment was available. In addition, the study failed to include suitable controls.

In a case study involving a nursing mother exposed daily for 30 to 60 minutes to unknown but excessive PCE concentrations, Bagnell and Ellenberger (1977) reported subjective complaints of dizziness.

6.1.4.2 Effects of Long-term Exposures--In a comprehensive 3-month chamber study of six males and six females, designed to elicit interactions between ethanol and diazepam (Valium®) and PCE, Stewart and coworkers (Stewart et al., 1977; Hake and Stewart, 1977) found that exposure to 25 and 100 ppm PCE (170 and 678 mg/m^3) alone or in combination with diazepam or alcohol had no effect on the EEG tracings. A battery of neurological and behavioral tests, consisting of the following, were administered at the peak blood levels of exposure: Michigan eye-hand coordination, rotary pursuit, Flanagan coordination, and Saccade eye, velocity, and dual attention tasks. EEG's were recorded for spectral density analysis during the exposures. The only decrement in the behavioral tests reported by the authors was a "non-consistent significant detrimental effect of PCE alone (100 ppm; 678 mg/m^3) in the performance of the Flanagan coordination test." This test requires subjects to follow a spiral pathway with a pencil, touching the sides of the pathway as few times as possible.

Each subject was exposed 5.5 hr/day. The exposure duration was 11 weeks. Monday and Tuesday were generally control days. Thursday was an intermediate exposure day. Wednesday and Friday were 100-ppm-PCE exposure days. No other unusual behavioral or neurological findings were noted for exposures to PCE alone. However, subjective complaints were noted for the nine subjects who completed the study. One subject accounted for one-third the incidence of headache complaints and two-thirds the incidence of nausea complaints reported.

The same subject complained of eye, nose, and throat irritation on all but 8 of the 55 test days. Analysis of the times of occurrence of these subjective symptoms revealed that there was no relationship to PCE vapor exposure. In fact, the incidence decreased somewhat when the 100-ppm-PCE (678 mg/m^3) exposure concentrations were compared to non-PCE exposures. The absence of EEG abnormalities, such as were found in an earlier study by Stewart and co-workers (1974), suggest that EEG observations may not be reliable indicators of early signs of PCE narcosis. In their earlier study, impairment of the Flanagan coordination test was also occasionally noted during exposures to 150 ppm for 7.5 hours. Chmielewski et al. (1976) observed abnormal EEG tracings in 10 of 16 individuals exposed occupationally, from 2 months to 27 years, to 59 to 442 ppm PCE (400 to 3000 mg/m^3). However, 6 of 16 cases were further diagnosed as pseudo-neurotic syndrome, and in 4 of 16 cases the researchers "were led to a diagnosis or suspicion at least of encephalopathy." No additional details were given.

Stewart et al. (1970) conducted an experiment with 16 healthy technical employees ranging in age from 24 to 64 years. Five of the male subjects, ranging in age from 36 to 64 years, were repeatedly exposed to 100 ppm (678 mg/m^3) PCE for 7 hours on 5 consecutive days. The remainder of the subjects were exposed for one 7-hour period. When queried every hour during the exposure about subjective response, 25 percent of the subjects reported that they had developed a mild frontal headache. Sixty percent complained of mild eye, nose, or throat irritation developing within the first 2 hours of exposure and usually subsiding before 7 hours had elapsed. Forty percent of the subjects reported that they felt "slightly sleepy" when inactive in the chamber. The authors wrote, "Unfortunately, it was not possible to confine these same subjects in the exposure chamber for a comparable control period, so the clinical significance of the slightly sleepy sensation cannot be assessed." Twenty-five percent of the subjects "noted some difficulty in speaking, analogous to that noted during the early phases of intoxication." The single untoward objective response was an abnormal Romberg test occurring in three of the subjects within the first 3 hours of exposure to 100 ppm (678 mg/m^3). With greater mental effort, these three individuals were able to perform a normal test when given a second chance. Those subjects repeatedly exposed had fewer subjective complaints. One subject, who had low-grade chronic sinusitis, developed a mild frontal headache during the course of each exposure. Two out of five subjects consistently reported mild eye and throat irritation and lightheadedness. Sensations of sleepiness and speech difficulty were not reported. All other neurological test results were normal. The group exposed repeatedly responded more comparably to subjects in two subsequent, more sophisticated 3-week studies performed by Stewart et al. (1974 and 1977) with repeated exposure to 100 ppm (678 mg/m^3) PCE alone and in combination with either diazepam or ethanol.

Similar subjective complaints, as well as neurological effects, of PCE also were reported in other studies (Method, 1946; Lob, 1957; Eberhardt and Freundt, 1966; Gold, 1969).

6.2 ANIMALS

Reported toxic effects associated with PCE exposure in laboratory animals include effects on the CNS, cardiovascular system, skin, liver, kidney, and the immune system.

A number of previous reviews (NIOSH, 1976; Fuller, 1976; U.S. Environmental Protection Agency, 1980; Walter et al., 1976; Parker et al., 1978; Fishbein, 1976; U.S. Environmental Protection Agency, 1977) support the assessment of the toxic effects of PCE in animals as presented below. Summaries of these toxic effects and of toxic dose data appear in Tables 6-1 and 6-2.

6.2.1 Effects on the Nervous System

Effects of acute exposure to PCE are very much dominated by CNS depression. Abnormal weakness, handling intolerance, intoxication, restlessness, irregular respiration, muscle incoordination, unconsciousness, and ultimately, death are among the symptoms, considered to be manifestations of effects on the CNS, which have been observed in animals exposed to excessive levels.

Symptoms of acute CNS depression have been seen in experimental animals (National Institute of Occupational Safety and Health, 1976; Fuller, 1976; U.S. Environmental Protection Agency, 1980; Walter et al., 1976; Parker et al., 1978; Fishbein, 1976; U.S. Environmental Protection Agency, 1977) and in dogs treated with therapeutic (anthelmintic) doses of PCE (Miller, 1966; Snow, 1973; Christensen and Lynch, 1973) PCE.

Rowe et al. (1952) reported that behavioral changes were not observed in rats, guinea pigs, rabbits, or monkeys exposed repeatedly for 7 hr/day at vapor concentrations of PCE up to 401 ppm (2720 mg/m^3).

TABLE 6-1. SUMMARY OF THE EFFECTS OF TETRACHLOROETHYLENE ON ANIMALS

Animal species	Dose concentration	Route of administration	Exposure variables	Effects	Reference
Rabbit (female)	N/A	skin	single application single instillation (eye)	primary eye and skin irritant	Duprat et al., 1976
Rabbit	13 mmole/kg	oral	single dose	marked increase in serum enzymes, i.e., alkaline phosphatase, SGOT, and SGPT within 24 hours	Fujii et al., 1975
Mouse	200 ppm	inhalation	4 hours single exposure	moderate fatty infiltration of the liver 1 day after exposure but not 3 days after	Kylin et al., 1963
Mouse	200 ppm	inhalation	4 hours/day 6 days/week 1-8 weeks	fatty degeneration of the liver	Kylin et al., 1965
Guinea pig	100 ppm	inhalation	7 hours/day 5 days/week 132 exposures	increased liver weights in females	Rowe et al., 1952
Guinea pig	200 ppm	inhalation	7 hours/day 5 days/week	increased liver weights with some fatty degeneration in both males and females - slight increase in lipid content and several small fat vacuoles in liver	Rowe et al., 1952
Guinea pig	400 ppm	inhalation	7 hours/day 5 days/week 169 exposures	more pronounced liver changes than at 200 ppm, slight cirrhosis was observed - increased liver weight, increase in neutral fat and esterified cholesterol in the liver, moderate central fatty degeneration, cirrhosis	Rowe et al., 1952

TABLE 6-1. (continued)

Animal species	Dose concentration	Route of administration	Exposure variables	Effects	Reference
Guinea pig	2500 ppm	inhalation	18 7-hour exposures	loss of equilibrium, coordination, and strength, increase in weights of liver and kidney, fatty degeneration of the liver, cloudy swelling of tubular epithelium of the kidney	Rowe et al., 1952
Rabbit Rat Monkey	100-400 ppm	inhalation	7 hours/day 5 days/week 6 months	no abnormal growth, organ function, or histopathologic findings	Rowe et al., 1952
Rabbit	2500 ppm	inhalation	28 7-hour exposures	central nervous system depression without unconsciousness	Rowe et al., 1952
Rat	2500 ppm	inhalation	1-13 7-hour exposures	loss of consciousness and death	Rowe et al., 1952
Rat	1600 ppm	inhalation	18 7-hour exposures	drowsiness, stupor, increased salivation, extreme restlessness, disturbance of equilibrium and coordination, biting and scratching reflex	Rowe et al., 1952
Rat	3000-6000	inhalation	single exposure up to 8 hours	increase in liver weight, increase in total lipid content of liver accompanied by a few diffusely distributed fat globules	Rowe et al., 1952
Rabbit	15 ppm	inhalation	3-4 hours/day 7-11 months	depressed agglutinin formation	Mazza, 1972
Rabbit	2212 ppm (15 mg/l)	inhalation	45 days 4 hrs/day 5 days/week	liver damage indicated by elevated SGPT, SGOT, SGLDH: marked reduction of Schmidt index	Mazza, 1972

TABLE 6-1. (continued)

Animal species	Dose concentration	Route of administration	Exposure variables	Effects	Reference
Rat	70 ppm	inhalation	8 hours/day 5 days/week 150 exposures (7 months)	no pathological findings	Carpenter, 1937
Rat	230 ppm	inhalation	8 hours/day 5 days/week 150 exposures (7 months)	similar, but less severe, pathological findings as with 470 ppm - congestion and light granular swelling of kidneys	Carpenter, 1937
Rat	470 ppm	inhalation	8 hours/day 5 days/week 150 exposures (7 months)	congested livers with cloudy swelling, no evidence of fatty degeneration or necrosis: evidence of kidney injury - increased secretion, cloudy swelling, and desquamation of kidneys: congestion of spleen	Carpenter, 1937
Rat	2750-9000 ppm	inhalation	single exposure	no deaths	Carpenter, 1937
Rat	19000 ppm	inhalation	30-60 minutes	congested livers with granular swelling, some deaths	Carpenter, 1937
Rabbit	15 ppm	inhalation	3-4 hours/day 7-11 months	moderately increased urinary urobilinogen, pathomorphological changes in the parenchyma of liver and kidneys	Navrotskii et al., 1971
Rabbit	2211 ppm (15 mg/l)	inhalation	45 days	significant reduction of glomerular filtration rate and the renal plasma flow; decrease of highest excretory tubular capacity (kidney damage)	Brancaccio et al., 1971

TABLE 6-1. (continued)

Animal species	Dose concentration	Route of administration	Exposure variables	Effects	Reference
Mouse (Swiss male, 10 animals)	2.5 ml/kg	intraperitoneal		100 mg percent or more protein found in one of six mice - proximal convoluted tubules were swollen in all animals and necrotic in one	Plaa and Larson, 1965
Mouse (10 Animals)	5.0 ml/kg	intraperitoneal		two of four mice had 100 mg percent or more protein in urine	
		(urine samples were collected 24 hours post-injection)			
Rabbit	2211 ppm (15 mg/l)	inhalation	45 days	increased plasma and urine levels of adrenal cortical and adrenal medullar hormones; increased excretion of principal catecholamine metabolite (not statistically significant)	Mazza and Brancaccio, 1971
Mouse	N/A	intraperitoneal		liver dysfunction	Klaassen and Plaa, 1966
Mouse	N/A	intraperitoneal		LD_{50}	Klaassen and Plaa, 1966
Dog		intraperitoneal		elevated SGPT	Klaassen and Plaa, 1967
Dog		intraperitoneal		caused phenolsulfonephthalein retention indicating kidney dysfunction	Klaassen and Plaa, 1967
Dog		intraperitoneal		LD_{50}	Klaassen and Plaa, 1967
Rat	300 ppm	inhalation	7 hours/day days 6-15 of gestation	decreased maternal weight gains, increased fetal reabsorptions	Schwetz et al., 1975

TABLE 6-1. (continued)

Animal species	Dose concentration	Route of administration	Exposure variables	Effects	Reference
Mouse	300 ppm	inhalation	7 hours/day days 6-15 of gestation	maternal liver weights increased relative to body weight; increased incidences of fetal subcutaneous edema, delayed ossification of skull bones, and split sternebrae	Schwetz et al., 1975
Rat	44.2 ppm	inhalation	entire gestation period	decreased levels of DNA and total nucleic acids in the liver, brain, ovaries, and placenta	Aninina, 1972
Mouse	15-74 ppm	inhalation	5 hours/day 3 months	decreased electroconductance of muscle and "amplitude" of muscular contraction	Dmitrieva, 1968
Rat	15 ppm	inhalation	4 hours/day 5 months	EEG changes and protoplasmal swelling of cerebral cortical cells, some vacuolated cells and signs of karyolysis	Dmitrieva, 1966
Rat	73 and 147 ppm	inhalation	4 hours/day 4 weeks	EEG and electromyogram changes; decreased acetylcholinesterase activity	Dmitrieva, 1966
Dog (male beagles)	0.5-1.0% v/v 5000 & 10000 ppm	inhalation	7 minutes house air followed by 10 minutes of tetrachloroethylene 8 μg/kg epinephrine given I.V. (1) a control dose after 2 minutes of breathing air (2) challenge dose after 5 minutes of breathing test compound	cardiac sensitization (development of serious arrhythmia or cardiac arrest) was not induced at the concentrations tested (other similar compounds gave positive results at same concentration,	Reinhardt et al., 1973

TABLE 6-1. (continued)

Animal species	Dose concentration	Route of administration	Exposure variables	Effects	Reference
Cat	3000 ppm	inhalation	4 hours	no anesthesia	Lehmann, 1911
Cat	14,600 ppm	inhalation	1-2 hours	anesthesia	Lehmann and Schmidt-Kehl, 1936
Mouse	40 mg/1 5,900 ppm	inhalation		minimal fatal concentration	Lamson et al., 1929
Mouse	4-5 ml/kg	oral		death in 2-9 hours from central nervous system depression	Lamson et al., 1929
Rabbit	5 ml/kg	oral (in oil)		death in 17-24 hours	Lamson et al., 1929
Cat	4 mg/kg	oral (in oil)		death within hours	Lamson et al., 1929
Dog	9000 ppm	inhalation		narcosis, marked salivation, "narrow margin of safety"	Lamson et al., 1929
Dog	4-25 ml/kg	oral (in oil)		death in 5-48 hours	Lamson et al., 1929

TABLE 6-2. TOXIC DOSE DATA

Description of exposure[a]	Species	Route of administration	Dose concentration	Toxic effect endpoint	Time	Reference
LD$_{50}$	mouse (male)	oral	8100 mg/kg	death	36 hr	Wenzel and Gibson, 1951
LD$_{50}$	mouse	interperitoneal	2.9 ml/kg 28 mM/kg 4700 mg/kg	death	24 hr	Klaassen and Plaa, 1966
ED$_{50}$	mouse	interperitoneal	2.9 ml/kg 28-32 mM/kg	liver dysfunction		
LD$_{50}$	mouse	interperitoneal	34 mM/kg	death	24 hr	Gehring, 1968
ED$_{50}$	mouse	interperitoneal	24 mM/kg	liver toxicity		
LD$_{50}$	dog	interperitoneal	2.1 ml/kg 21 mM/kg 3400 mg/kg	death	24 hr	Klaassen and Plaa, 1967
ED$_{50}$	dog	interperitoneal	0.74 ml/kg 7.2 mM/kg	liver damage	24 hr	Klaassen and Plaa, 1967
ED$_{50}$	dog	interperitoneal	1.4 ml/kg	kidney dysfunction	24 hr	Klaassen and Plaa, 1967
LD$_{50}$	mouse	subcutaneous	390 mM/kg	death	10 days	Plaa et al., 1958
ED$_{50}$	mouse	subcutaneous	27 mM/kg	liver toxicity		Plaa et al., 1958
LD$_{50}$	mouse	oral (undiluted)	0.109 ml	death	unknown	Dybing and Dybing, 1946
LD$_{50}$	mouse	oral (in oil)	0.134 ml	death	unknown	Dybing and Dybing, 1946
LD$_{50}$	mouse	oral	8850 mg/kg	death	unknown	Handbook of Toxicology, 1959
LCL$_{o}$	mouse	inhalation	23000 mg/m^3	death	2 hr	
LD$_{50}$	rat			death		Withey and Hall, 1975

TABLE 6-2. (continued)

Description of exposure[a]	Species	Route of administration	Dose concentration	Toxic effect endpoint	Time	Reference
LCL_o	rat	inhalation	4000 ppm	death	4 hr	Handbook of Toxicology, 1959
LCL_o	rat	inhalation	4000 ppm	death	4 hr	
LDL_o	dog	oral	4000 mg/kg	death	unknown	Arch. Hyg. Bakteriol. 116:131, 1936
LDL_o	dog	intravenous	85 mg/kg	death	unknown	Carpenter et al., 1949
LDL_o	cat	oral	4000 mg/kg	death	unknown	Clayton, 1962
LDL_o	rabbit	oral	5000 mg/kg	death	unknown	Lamson et al., 1929

[a] LCL_o - the lowest concentration of a substance, other than an LC_{50}, in air which has been reported to have caused death in humans or animals.

LDL_o - the lowest dose of a substance, other than an LD_{50}, that is introduced by any route other than inhalation over any given period of time and reported to have caused death in humans or animals introduced in one or more divided portions.

A single 4-hour exposure to 2270 ppm PCE (15400 mg/m^3) caused rats to suffer an 80-percent loss of both avoidance and escape responses (Goldberg et al., 1964). Savolainen et al. (1977) demonstrated behavioral impairment in rats exposed to 200 ppm (1357 mg/m^3) PCE vapor for 6 hr/day for 4 days. Marked increases in the frequency of ambulation in the open field were most significant 1 hour after exposure when these responses were compared to control responses. High tissue concentrations of PCE were detected in fat and brain tissue after a relatively short exposure. A significant decrease in the ribonucleic acid (RNA) content of the brain was measured as well as an increase in nonspecific cholinesterase activity.

Dmitrieva and coworkers (Dmitrieva, 1966; Dmitrieva and Kuleshov, 1971; Dmitrieva et al., 1968; Dmitrieva, 1973; Dmitrieva, 1968) have reported alterations of EEG patterns in rats exposed to as low as 15 ppm PCE (102 mg/m^3) 3 to 4 hr/day for 7 to 11 months. Such effects have not been observed by Western investigators at much higher levels nor were details provided in the reports of these Russian investigators to adequately assess the quality of the studies.

6.2.2 Effects on the Liver and Kidney

PCE is generally regarded as being both hepatotoxic and nephrotoxic when exposure is excessive and prolonged.

Carpenter (1937) exposed three groups of 24 albino rats each to PCE vapor concentrations averaging 70, 230, or 470 ppm (475, 1560, or 3188 mg/m^3) for 8 hr/day, 5 days/week, for up to 7 months. The maximum exposure for any animal during the 7-month period was 150 days (1200 hours). A group of 18 unexposed animals served as controls.

The rats exposed to 470 ppm (3188 mg/m^3) for 150 days followed by a 46-day rest period developed cloudy and congested livers with swelling; there was no evidence of fatty degeneration or necrosis. These rats also had increased renal secretion with cloudy swelling and desquamation of kidneys, as well as congested spleens with increased pigment. The pathologic changes were similar but less severe in the rats exposed to 230 ppm PCE (1560 mg/m^3). In some instances, there was congestion and light granular swelling of the kidneys after 21 exposure days. After 150 days of exposure, followed by a 20-day rest, congestion was found in the kidney and spleen. The livers showed reduced glycogen storage. Microscopic evidence of damage to liver, kidney, or spleen in rats exposed at 70 ppm (475 mg/m^3) for 150 days was not observed. In addition, microscopic examination of heart, brain, eye, or nerve tissue did not reveal any damaging effects in any of the chronically exposed rats. Functional parameters, including icteric index, Van den Bergh test for bilirubin, and blood and urine analysis, were normal after the exposures. Fertility of female rats, as measured by a fertility index (actual number of litters/possible number of litters), was increased slightly after repeated exposures to 230 or 470 ppm PCE (1560 or 3188 mg/m^3). No deaths or signs of anorexia or diminished activity were observed during the chronic exposures.

Carpenter also tried to determine the highest concentration of PCE vapor that would not anesthetize rats exposed for 8 hours. Exposure to 31,000 ppm (210,273 mg/m^3) was lethal within a few minutes. Rats exposed to 19,000 ppm (128,871 mg/m^3) died after 30 to 60 minutes. Animals that were exposed to 19,000 ppm (128,877 mg/m^3) and removed from the inhalation chamber just prior to unconsciousness developed congestion and granular swelling of the liver. Similar liver effects were seen after exposure at 9000 ppm (61,047 mg/m^3). There was also marked granular swelling of the kidneys. A single exposure at 9000, 4500, or 2750 ppm (61,047, 30,523, or 15,261 mg/m^3) did not cause death to any of the rats in this study; however, post-mortem examinations of the rats exposed to those concentrations revealed only a slight increase in the prominence of liver and kidney markings.

Rowe et al. (1952) exposed rabbits, monkeys, rats, and guinea pigs to PCE vapor for 7 hours, 5 days/week, for up to 6 months. Exposure concentrations ranged from 100 to 2500 ppm (678 to 16,957 mg/m^3). Three of the four species tested -- rabbits, monkeys, and rats -- showed no effects of repeated exposures to concentrations up to 400 ppm (2713 mg/m^3). There were no adverse effects on growth, liver weight, or lipid content, or gross or microscopic anatomy observed in any animal. In contrast, guinea pigs showed marked susceptibility to PCE in this study. The liver weights of female guinea pigs increased significantly after 132 7-hour exposures at 100 ppm (678 mg/m^3). At 200 ppm (1356 mg/m^3), there was a slight depression of growth in female guinea pigs and increased liver weights in both males and females. Slight to moderate fatty degeneration of the liver also was observed. These effects were more pronounced in guinea pigs that received 169 7-hour exposures at 400 ppm (2713 mg/m^3). At this concentration, there also were increased amounts of neutral fat and esterified cholesterol in livers. Gross and microscopic examination of the tissues revealed slight to moderate fatty degeneration in the liver with slight cirrhosis. Rowe et al. stated that at 395 ppm (2680 mg/m^3), increased kidney weights also were observed in guinea pigs but not in other species. Guinea pigs have been shown to be extremely sensitive to toxicity testing.

Klaassen and Plaa (1967) showed that intraperitoneal injections of PCE to mongrel male and female dogs can produce damage to the kidney and liver. They estimated the ED_{50} (effective dose in 50 percent of the animals tested) for liver and kidney damage as well as the 24-hour LD50 value (lethal dose in 50 percent of the animals treated). The ED_{50} values were measured by sulfobromophthalein (BSP), SGPT, glucose, protein, and phenolsulfonephthalein (PSP), indicators of liver or kidney dysfunction. The LD_{50} was 2.1 ml/kg (21 mmoles/kg) and the ED_{50} for elevation of SGPT was 0.74 ml/kg (7.2 mmoles/kg). The ED_{50} for diminution of PSP excretion was 1.4 ml/kg (14 mmoles/kg). After administration, effects on the liver and kidneys were determined by microscopic examination. At near-lethal doses, PCE produced moderate neutrophilic infiltrations in the sinusoids and portal areas; necrosis was not observed. Near the ED_{50}, vacuolization of centralobular hepatocytes in about half the animals was observed. After a single interperitoneal injection at 0.75 x LD_{50}, SGPT peaked at 2 days and rapidly declined throughout the 9-day measurement period. Kidney dysfunction was deemed significant when PSP excretion was less than 39 percent (determined 24 hours after interperitoneal injection). At near PSP excretion--ED_{50} doses, only mild dilation of the collecting ducts was seen in some of the kidneys.

In a similar study using Swiss-Webster mice, Klaassen and Plaa (1966) determined that the 24-hour LD_{50} was 2.9 ml/kg (28 mmoles/kg). The ED_{50} for BSP retention was 2.9 ml/kg (32 mmoles/kg). The ED_{50} for elevation of SGPT was 2.9 ml/kg (28 mmoles/kg). When ethanol (5 gm/kg) was administered by gavage for 3 days prior to injection of 1.0 ml/kg PCE, neither PSP excretion nor BSP retention was significantly altered. At BSP-ED_{50}, mice exhibited predominantly inflammatory changes with trace to marked quantities of lipid accumulation.

Effects upon the livers of rats exposed continuously for 3 months to 0.7 and 2.7 ppm (4.5 and 19 mg/m^3) were reported by Bonashevskaya (1977). In the low-exposure group, an increase in the activity of succinate dehydrogenase (SDH) was reported. At the high level, SDH was slightly decreased in the central lobular sections while activity in the peripheral zones was either unchanged or increased. The activities of glucose-6-phosphate dehydrogenase (G6PDH) were similar in pattern to that for SDH. RNA content was reported to be decreased. LDH activity was either unchanged or increased. The enzyme variations indicated the subject's adaptation to exposure. No significant histomorphological changes in the liver were reported at either exposure level.

A subcutaneous injection (0.4 ml daily, for 8 weeks) of PCE to groups of rats that were fed a diet containing high protein had less of an adverse effect upon the liver than PCE alone (Dumitrache et al., 1975). PCE was observed to induce liver hypertrophy compared to the reaction of the controls ($p < 0.001$). Hypertrophy was most pronounced in the low-protein group. In treating rats fed a diet containing low protein, cholesterol ($p < 0.001$) and total liver lipids ($p < 0.001$) were elevated compared to the reaction of the controls. Twelve rats were used in each of the four groups.

Kylin et al. (1963) noted moderate fatty degeneration of the liver with a single 4-hour exposure to 200 ppm PCE (1356 mg/m^3) in female albino mice that were sacrificed 1 day after exposure. Degeneration was not observed in mice sacrificed 3 days after exposure. The mice were exposed to PCE concentrations of 200, 400, 800, or 1600 ppm (1356, 2713, 5426, or 10,852 mg/m^3) for 4 hours. Tissues were studied microscopically to assess the extent of necrosis and fat infiltration of the liver. Moderate to massive infiltration was observed in mice killed 1 or 3 days after exposure at 400 ppm (2713 mg/m^3) or more, but no cell necrosis was observed even after 4 hours exposure up to 1600 ppm PCE (10,852 mg/m^3). Kylin et al. (1963) exposed four groups of 20 albino mice to 200 ppm PCE (1356 mg/m^3). Each group was exposed for 4 hr/day, 6 days per week, for 1, 2, 4, or 8 weeks. Microscopic examinations were performed on livers and kidneys of the exposed mice and controls. Fatty degeneration was particularly marked and tended to be more severe with longer exposure to PCE. Chemical determination of the liver fat content was performed in addition to the histologic examination. Correlation between the histologically evaluated degree of fatty degeneration and the concentration of extracted fat was +0.74. Liver fat content of the exposed animals was between 4 and 5 mg/g of body weight, as compared to 2 to 2.5 mg/g for the control animals. The actual fat content of the livers did not increase with duration of exposure as did the extent of the fatty infiltration. No liver cell necrosis was observed. No effect on the kidneys was reported.

Mazza (1972) exposed 15 male rabbits for 4 hr/day, 5 days a week, for 45 days, to 2790 ppm PCE (18,924 mg/m^3). Mazza looked at the effect of PCE on serum enzyme levels in an attempt to determine the specific location of initial liver injury as well as the severity of the damage to the liver. The Schmidt Index, which is the sum of SGOT and the SGPT divided by the serum glutamate dehydrogenase (GDH), was used as an indication of hepatic disorders. Enzymatic determinations were made before exposure and 15, 30, and 45 days after exposure to PCE. All three of the enzymes showed an increase in activity, but the GDH increased the most; GDH reduced the Schmidt Index from 6.70 to 1.79. Mazza concluded that this reduction indicates the prevalence of mitochondrial injury over cytoplasmic injury in the liver.

Mazza and Brancaccio (1971) exposed 10 rabbits for 4 hr/day, 5 days per week, for 45 days, to 2790 ppm PCE (18,924 mg/m^3). These investigators found a moderate, but not statistically significant, increase in levels of adrenal cortical and medullar hormones--plasma and urinary corticosteroids and catecholamines--including increased excretion of 3-methoxy-1-hydroxymandelic acid, the principal catecholamine metabolite.

In another study, Brancaccio et al. (1971) exposed 12 male rabbits for 4 hr/day, 6 days per week, for 45 days, to 2280 ppm PCE (15,465 mg/m^3) to look at effects on kidney function. They noted a reduction in glomerular filtration and renal plasma flow and a decrease in the maximum tubular excretion when measured upon cessation of the exposure regimen. Brancaccio et al. concluded that PCE causes kidney damage, primarily in the renal tubule. These findings agreed with earlier histological findings of Pennarola and Brancaccio (1968) in which kidney injury, following exposure to PCE, appeared to be primarily in the renal tubule.

Plaa and Larson (1965) dosed mice with PCE by interperitoneal injection. Ten mice received 2.5 mg/kg and 10 others received 5.0 mg/kg. Urine samples were collected from surviving mice 24 hours after the injection of PCE. Protein was found in the urine of one of the six surviving mice injected with the lower dose and in two of four survivors of the higher dose at levels of 100 or more mg percent. None of the survivors had greater than 150 mg percent glucose in the urine. The kidneys of the mice given the lower dose were examined microscopically. The proximal convoluted tubules were swollen in all animals and necrotic in one.

Fujii (1975) observed an increase in serum enzyme activities (i.e., alkaline phosphatase, SGOT, and SGPT) within 24 hours after a single dose of 13 mmole PCE/kg given orally to rabbits. These changes in serum enzyme activities, indicative of liver damage, were mild and transient.

6.2.3 Effects on the Heart

The possible cardiovascular effects of PCE have not been systematically investigated. Reinhardt et al. (1973) noted that PCE does not appear to sensitize the myocardium to epinephrine. In this study of dogs, a response that was considered to be indicative of cardiac sensitization was the development of a seriously life-threatening arrhythmia or cardiac arrest following a challenge dose of epinephrine. PCE inhalation exposure for 10 minutes at concentrations of 5000 or 10,000 ppm (33,915 or 67,830 mg/m^3) did not result in a positive response in any of the 17 dogs.

The investigators noted the possibility that PCE has the potential for cardiac sensitization, as do many organic solvents. However, the PCE concentration that failed to elicit a positive response (10,000 ppm) would be a level immediately hazardous to life, based on CNS effects.

Christensen and Lynch (1933) observed depression of the heart and respiration in five dogs, each given a single oral dose ranging from 4 to 5.3 ml/kg PCE (approximately the LD_{50} for dogs). Autopsy showed fatty infiltration of both heart and liver tissue. The small intestine was extremely shriveled and showed marked inflammation.

6.2.4 Effects on the Skin and Eye

Duprat et al. (1976) have shown PCE to be a primary eye and skin irritant in rabbits. Instillation of the chemical into the eye produced conjunctivitis with epithelial abrasion. However, healing of the ocular mucosa was complete within 2 weeks. PCE had a severe irritant effect when a single application was made to the skin of the rabbit.

6.3 ADVERSE EFFECTS OF SECONDARY POLLUTANTS

The level of phosgene derived from photodecomposition of PCE is not likely to result in serious long-term effects. In occupational settings or under certain conditions in which phosgene is directly formed at high temperatures from halocarbons (cigarette smoke, welding), sufficient warning from the generation of extremely irritating hydrogen chloride vapors would prevent exposure to harmful concentrations of phosgene.

6.4 SUMMARY OF ADVERSE HEALTH EFFECTS AND ASSOCIATED LOWEST OBSERVABLE EFFECT CONCENTRATIONS

6.4.1 Inhalation Exposure

A number of case reports describe accidental or occupational exposure to PCE. However, the duration and extent of exposure either were unknown or involved excessively high concentrations. The few controlled human studies available generally provide information on effects resulting from short-term exposures at levels near 100 ppm (678 mg/m^3). Effects associated with chronic exposures, on the other hand, are available from animal experiments.

6.4.1.1 Effects Associated With Intermittent or Prolonged Exposure--The data available from both human and animal exposures to excessive concentrations of PCE indicate that the CNS, liver, and kidneys may be adversely affected. In a controlled study involving humans, Stewart and coworkers (1977) exposed 12 individuals to 25 and 100 ppm PCE (170 and 678 mg/m^3), 5.5 hr/day, for 3 months (55 exposures). At 100 ppm PCE (678 mg/m^3) there was a non-consistent detrimental effect upon coordination, as measured by the Flanagan test, but no adverse effects on the remainder of a battery of neurological and behavioral tests and no alterations in the EEG patterns. There were no observed effects at 25 ppm (170 mg/m^3).

Both subchronic and chronic inhalation exposures of animals support the observations in humans. Carpenter (1937) observed dose-related congestion and swelling in the livers and kidneys of rats exposed for 8 hr/day, 5 days per week, for 7 months, to 230 and 470 ppm (1559 and 3187 mg/m^3). Rowe et al. (1952) observed degenerative changes in the livers of guinea pigs, a species that appears more sensitive to PCE, following an 8-month exposure to 200 and 400 ppm (1356 and 2712 mg/m^3), for 7 hr/day, 5 days per week.

Carpenter (1937) reported a no-observable-effects level (NOEL) at 70 ppm PCE (475 mg/m^3) in rats exposed 8 hr/day, 5 days per week, for 7 months. Histologic examination of the liver, kidneys, spleen, heart, brain, eye, and nerve tissue, as well as blood and urine analyses, were performed. The NOEL is defined as that exposure level at which there are no statistically significant increases in frequency or severity of effects between the exposed population and the appropriate control.

6.4.1.2 Effects Associated With Short-term Exposure--Controlled studies in humans have provided information on a progression of effects upon the CNS, ranging from lightheadedness to narcosis, and subsequently to death. A summary of the estimated dose-response relationships for acute effects of single, short-term exposures of humans is presented below:

>4000 ppm PCE:	possibly life-threatening
2000 ppm PCE:	light narcosis, possible liver damage
1000 ppm PCE:	lightheadedness

200 ppm PCE: possible reversible fatty changes in the liver
100 ppm PCE: possible first signs of CNS depression, giddiness, slight eye irritation
75 ppm PCE: very slight eye irritation
5 ppm PCE: odor threshold

Stewart et al. (1970) reported lightheadedness in 25 percent of the 15 volunteers exposed for 7 hours to an average PCE concentration of 101 ppm (685 mg/m^3). Two subsequent studies by Stewart et al. (1974, 1977), using more updated technology and testing methodology, did not confirm this result even when exposures to 100 ppm PCE were combined with diazepam or alcohol. Rowe et al. (1952) reported lightheadedness in four individuals exposed for 2 hours to 216 ppm PCE (1465 mg/m^3), but not in six individuals exposed 2 hours to 106 ppm (719 mg/m^3). The observations in these studies follow the expected pattern for a non-specific anesthetic effect. These results show that a short-term exposure to PCE in the range of about 100 to 200 ppm (678 to 1356 mg/m^3) will result in some individuals experiencing the first gross signs of CNS depression and behavioral alterations. Test results also indicate that short-term exposures may damage the liver. Kylin et al. (1963) reported transient moderate fatty infiltration in livers of mice exposed for 4 hours to 200 ppm PCE (1356 mg/m^3). However, liver damage in humans is generally associated with short-term exposures greatly in excess of 100 ppm (678 mg/m^3).

6.4.2 Oral Exposure

As summarized in Table 6-2, the acute oral toxicity of PCE has been determined in rats, mice, cats, rabbits, and dogs. There are no subchronic oral exposure studies and only one chronic study--the NCI bioassay. Neither of these studies identifies either a NOEL or lowest-observed-adverse-effect level (LOAEL).

6.4.3 Dermal Exposure

Although PCE can be absorbed through unbroken skin, absorption was estimated to be minor (Stewart and Dodd, 1964). Toxic quantities would probably not be absorbed through this route.

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7. TERATOGENICITY, EMBRYOTOXICITY, AND REPRODUCTIVE EFFECTS

Because of its widespread use, PCE has been studied for teratogenic potential. Teratology studies have been performed in rats, mice, and rabbits, using doses of PCE which, in some studies, produced slight signs of maternal toxicity. Other studies in chicken embryos (Elovaara et al., 1979) have indicated that PCE disrupts embryogenesis in a dose-related manner. However, since administration of PCE directly into the air space of chicken embryo is not comparable to administration of dose to animals with a placenta, it is not possible to interpret this result in relationship to the potential of PCE to cause adverse effects in animals or humans.

The following discussion of studies subscribes to the basic viewpoints and definitions of the terms "teratogenic" and "fetotoxic" as summarized and stated by the U.S. Environmental Protection Agency (1980):

> Generally, the term "teratogenic" is defined as the tendency to produce physical and/or functional defects in offspring _in utero_. The term "fetotoxic" has traditionally been used to describe a wide variety of embryonic and/or fetal divergences from the normal which cannot be classified as gross terata (birth defects) -- or which are of unknown or doubtful significance. Types of effects which fall under the very broad category of fetotoxic effects are death, reductions in fetal weight, enlarged renal pelvis edema, and increased incidence of supernumerary ribs. It should be emphasized, however, that the phenomena of terata and fetal toxicity as currently defined are not separable into precise categories. Rather, the spectrum of adverse embryonic/fetal effects is continuous, and all deviations from the normal must be considered as examples of developmental toxicity. Gross morphological terata represent but one aspect of this spectrum, and while the significance of such structural changes is more readily evaluated, such effects are not necessarily more serious than certain effects which are ordinarily classified as fetotoxic--fetal death being the most obvious example.
>
> In view of the spectrum of effects at issue, the Agency suggests that it might be useful to consider developmental toxicity in terms of three basic subcategories. The first subcategory would be embryo or fetal lethality. This is, of course, an irreversible effect and may occur with or without the occurrence of gross terata. The second subcategory would be teratogenesis and would encompass those changes (structural and/or functional) which are induced prenatally, and which are irreversible. Teratogenesis includes structural defects apparent in the fetus, functional deficits which may become apparent only after birth, and any other long-term effects (such as carcinogenicity) which are attributable to _in utero_ exposure. The third category would be embryo or fetal toxicity as comprised of those effects which are potentially reversible. This subcategory would therefore include such effects as weight reductions, reduction in the degree of skeletal ossification, and delays in organ maturation.

Two major problems with a definitional scheme of this nature must be pointed out, however. The first is that the reversibility of any phenomenon is extremely difficult to prove. An organ such as the kidney, for example, may be delayed in development and then appear to "catch up." Unless a series of specific kidney function tests are performed on the neonate, however, no conclusion may be drawn concerning permanent organ function changes. This same uncertainty as to possible long-lasting aftereffects from developmental deviations is true for all examples of fetotoxicity. The second problem is that the reversible nature of an embryonic/ fetal effect in one species might, under a given agent, react in another species in a more serious and irreversible manner.

7.1 ANIMAL STUDIES

7.1.1 Mice

Schwetz et al. (1975) reported a study of Swiss-Webster mice exposed to PCE via inhalation at concentrations of 300 ppm (2034 mg/m^3) for 7 hours daily on days 6 through 15 of presumed gestation. Day 0 of gestation was designated the day a vaginal plug was observed. This concentration was cited as twice the maximum allowable exclusion limit for human industrial exposure, with the Threshold Limit Value (TLV)® of 100 ppm (678 mg/m^3). Concurrent controls were exposed to filtered air.

Following maternal Caesarean-sectioning on day 18 of gestation, all fetuses were examined for external anomalies. One-half the fetuses were examined for soft tissue malformations using a free-hand sectioning technique, and the other one-half of the fetuses were cleared, stained, and examined for skeletal malformations. One fetus in each litter was processed and examined, using histopathological techniques. Seven litters were examined. The pups in the exposed group were significantly smaller, as measured by decreases in fetal body weight. Also, slight but not statistically significant increases in the number of runts were observed, as well as increases in the numbers of fetuses with subcutaneous edema, delayed ossification of the skull, delayed ossification of the sternebrae, and splits in sternebrae. No other remarkable malformations were reported in fetuses. Increases in the absolute and relative mean maternal liver weights were reported. No evidence of teratogenicity of PCE was found at the concentration tested.

7.1.2 Rats

Schwetz et al. (1975) also administered PCE to Sprague-Dawley rats by inhalation (300 ppm; 2034 mg/m^3) for 7 hours daily, on days 6 to 15 of gestation. Control rats were exposed to filtered air. Day 0 of gestation was designated as the day when spermatozoa were observed in smears of vaginal contents. Rats were sacrificed on day 21 of gestation. Caesarean sections were performed, and fetuses were examined for external malformations. One-half of the fetuses in each litter was examined for soft tissue malformations and the remaining one-half of the fetuses were examined for skeletal malformations. One fetus from each litter was randomly selected for serial sectioning and histological evaluation. Average maternal body weight gain was slightly reduced in the rats exposed to PCE. A slight but statistically significant increase in resorption was reported in 9 of 17 PCE-exposed litters evaluated. Exposure of dams to PCE produced no effect on the average number of implantations per litter, fetal sex ratios, or fetal body measurements. No soft tissue or skeletal anomalies were reported in the offspring of rats exposed to PCE. No evidence of teratogenicity of PCE was found at the concentration tested.

Beliles et al. (1980) exposed Sprague-Dawley rats to PCE at 300 ppm (2034 mg/m^3) for 7 hours daily, 5 days per week. Controls were administered filtered air. One-half of the rats were exposed for 3 weeks prior to mating. All rats were exposed during gestation on either days 0 through 18 or days 6 through 18, with day 0 designated as the day when spermatozoa were observed in smears of vaginal contents. It should be noted that the information in the report indicated that a Monday through Friday treatment period was used. It is unclear, based on information in the report, if the rats were indeed exposed on the gestational days cited. Three rats (days 6-18) died on the second day of pregestational treatment. Signs of ataxia and loss of balance were observed in all of the other rats of this group on the same day. The authors thought this response was most likely due to the high levels in the inhalation chamber during the last 2 hours of the day. Measurements taken 15 minutes before the end of the exposure showed 568 ppm (4061 mg/m^3) but could have been higher previously. The maternal body weight gain in the PCE-treated rats was not statistically different from that in controls during the pregestational period. Inhibition of maternal body weight gain occurred during the first week, as well as increases in mean absolute, but not relative, kidney and liver weights. No embryotoxic effects were observed which were attributable to maternal exposure to PCE, except for delays in skeletal ossification. This effect, however, is thought to be a reversible effect and is not considered a malformation as such. No teratogenic effects were observed.

Nelson et al. (1980) evaluated the ability of PCE to elicit a behavioral teratogenic response in Sprague-Dawley rats. In a pilot dose-range finding study, groups of 3 rats were exposed by inhalation to 1800 or 3600 ppm (12,204 or 24,408 mg/m^3) PCE. Narcotization was observed in dams. Therefore, a concentration of 900 ppm (6102 mg/m^3) PCE was used in the pilot study. Signs of maternal toxicity such as severe reductions in average food intake and decreased average body weight gain were observed. Food consumption and body weight gain were also reduced but were not statistically significant in rats exposed to 900 ppm (6102 mg/m^3) PCE on days 14 to 20 of gestation. Dams and pups exposed to 100 ppm (678 mg/^{3}) PCE on days 14 to 20 of gestation did not show any adverse effects as compared to the controls.

In the behavioral testing study, 102 pregnant rats were exposed to PCE by inhalation as follows:

(1) 900 ppm, days 7-13 of gestation (N=19)
(2) 900 ppm, days 14-20 of gestation (N=21)
(3) sham exposed, days 7-13 of gestation (N=13)
(4) sham exposed, days 14-20 of gestation (N=19)
(5) 100 ppm, days 14-20 of gestation (N=15)
(6) sham exposed, days 14-20 of gestation (N=15)

Seven behavioral tests were performed on days 4 through 46 postparturition, using one male and one female per litter. One group of rats, consisting of a male/female pair from each litter, was tested for ascent on a wire mesh screen and rotorod balancing. One male and one female rat per litter were tested for open-field activity, activity wheel, and avoidance conditioning. A third pair was tested for operant conditioning. Catecholamines (norepinephrine and dopamine), acetylcholine, and protein, measured in the brain tissue, were evaluated in 10 pups (no more than 2 per litter per treatment group) at birth, or at 21 days postparturition. Histopathological evaluation of brains for neuropathology was performed in an unreported number of pups.

Rats from dams exposed to 900 ppm (6102 mg/m^3) PCE on days 7 to 13 of gestation, performed less well on discrete testing of ascent and rotorod tests, but only on certain days of testing. Offspring exposed to 900 ppm (6102 mg/m^3) on days 14 to 20 of gestation performed less well on one test day in the ascent test, but later performed better than controls in the rotorod test, and were relatively more active than controls in the open-field tests. Acetylcholine levels were reduced in 21-day-old rats of dams exposed to 900 ppm

($6102\ mg/m^3$) PCE. Dopamine levels were reduced in rats of dams exposed on days 7 to 13 of gestation.

In the group of rats exposed to 100 ppm ($678\ mg/m^3$) PCE during days 14-20 of gestation, no significant differences were observed between the offspring of these animals and their controls on any of the behavioral tests. The authors summarized that "there were generally few behavioral or neurochemical differences observed between offspring of animals exposed to 900 ppm ($6102\ mg/m^3$) PCE during either days 7-13 or 14-20 of gestation. When significant differences did appear, they occurred more often when the group exposed during days 14-20 of gestation was compared with its control group."

It should be noted that the field of behavioral teratology is in its early stages of development (Buelke-Sam and Kimmel, 1979), and such behavioral alterations cannot at this time be interpreted in terms of human effect. It also must be noted that these observed changes may be related to maternal toxicity and do not represent a direct toxic effect.

Tepe et al. (unpublished, 1982) exposed Long-Evans hooded female rats to 1000 ± 125 ppm ($6780 \pm 847\ mg/m^3$) PCE vapors to ascertain if exposure before mating and during pregnancy was more detrimental to the embryo than exposure during pregnancy alone. Four treatment groups (30 rats each) were utilized in a two-by-two factorial design: exposure to PCE for two weeks (6 hours daily, 5 days per week) before mating, through day 20 of pregnancy; PCE before mating and filtered air during pregnancy; filtered air before and PCE during pregnancy; and filtered air throughout. One-half the dams in each treatment group were sacrificed on day 21 by ether anesthesia. Elevations in relative maternal liver weights and reduction in fetal body weight were observed without alteration in maternal weight gains in groups exposed during pregnancy. An excess of skeletal variations were seen in the group exposed before mating and during pregnancy; and excessive soft tissue variations (e.g. kidney dysplasia) occurred in the group exposed during pregnancy alone. These effects are consistent with embryotoxicity. Elevation in ethoxycoumaren dealkylase activity (an indicator of P_{450} activity) was observed in maternal livers but not fetal livers with pregnancy exposure. Ethoxyresorufin dealkylase activity (an indicator of P_{448} activity) was not elevated in maternal livers with PCE exposure and was not detectable in fetal livers. No other effects were observed in pregnant rats exposed for 6 h per day on days 0-20 of gestation.

Manson et al. (unpublished, 1982) conducted a study on postnatal evaluation of offspring of the female rats exposed to 1000 ± 125 ppm ($6780 \pm 847\ mg/m^3$) PCE before and/or during pregnancy. The four treatment groups are those described above (Tepe et al., 1982). The purpose of the postnatal evaluation was to determine if the reduction in body weight or the excess skeletal and soft tissue variants observed in term fetuses from the Tepe et al. (1982) study persisted, and if PCE possessed transplacental carcinogenic activity or neurobehavioral toxicity. Weight gain and survival of offspring up to 18 months of age, and frequency of any gross lesions observed at 6- and 18-month autopsies, were not influenced by prenatal exposure to PCE. Neurobehavioral tests of general activity in open field tests at 10 and 20 days of age, and in running wheels from 40 to 100 days of age, did not indicate treatment-related effects. Likewise, results from the visual discrimination test on offspring from 130 to 170 days of age were negative. Prenatal exposure to PCE did not exert a detrimental effect on any of the parameters of postnatal maturation examined.

7.1.3 Rabbits

Beliles et al. (1980) also investigated the teratogenic potential of PCE in rabbits. The rabbits were divided into six groups as follows:

Group	Conc (ppm)	Days of Exposure Pregestational	Gestational
1	0 (control)	none	0-21
2	0 (control)	5 days/week; 3 weeks	0-21
3	500	none	0-21
4	500	5 days/week; 3 weeks	0-21
5	500	none	0-21
6	500	5 days/week; 3 weeks	0-21

After the pregestational exposure period was complete, rabbits from each group were mated. A positive identification of spermatozoa in the vaginal canal was taken as evidence of mating and designated as day 0 of gestation. The two control groups (1 and 2) were exposed to filtered air and the exposure groups (3, 4, 5, and 6) to 500 ppm (3390 mg/m^3) PCE, 7 h per day. It is unclear if the animals were exposed on each day, i.e., on days 0 through 21 of gestation or only on a Monday through Friday basis. All rabbits could not have been mated on the same calendar day; thus, all rabbits would not have been at the same stage of gestation during the exposure period.

Mean body weights of rabbits during pregestational and gestational exposure indicated no significant difference between controls and treated groups. Reduced food consumption during the approximate period of days 10 through 22 of gestation was observed in groups 3 and 5 and may have been related to PCE exposure. During the investigation, 21 female rabbits died (9 in the control groups and 12 in the treatment groups). Placental abnormalities were found at all exposure levels. In four litters examined in group 5, 19 anomalies were found ($p < 0.05$ compared to group 1 and 2 controls.) Rank Sum analysis did not confirm this significance and the authors judged it to reflect a change confined to a few litters. Fifteen of the 19 abnormal placentas in group 5 occurred in two litters. Histopathologic evaluation failed to reveal any significant change in the placentas. Of the skeletal changes noted in the fetuses examined in each group, neither the frequency nor the character of changes in the treated groups indicated an adverse effect on fetal growth and development, nor any teratogenic effects.

7.2 SUMMARY

The mammalian animal tests performed to date do not indicate any significant teratogenic potential of PCE. On this basis, there is no evidence that suggest that the conceptus is uniquely susceptible to the effects of PCE. The anatomical effects observed reflect delayed development and can be considered reversible. The minor behavioral changes observed probably reflect maternal nutritional deprivation rather than a direct effect of PCE. It is important to note, however, that the reversible nature of an embryonic/fetal effect in one species might, in another species, be manifested in a more serious and irreversible manner. Thus, the teratogenic potential of PCE for humans must be considered unknown.

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8.1 MUTAGENICITY

The objective of this mutagenicity evaluation is to determine whether tetrachloroethylene has the potential to cause mutations in germ and somatic cells of humans. This qualitative assessment is based on data derived from several short-term tests that measure different types of genetic alterations: gene mutation, chromosomal aberrations, unscheduled DNA synthesis, and mitotic recombination (Table 8-1). These tests were conducted using bacteria, *Drosophila*, yeast, cultured mammalian cells, whole mammal systems, and cytogenetic analyses of exposed humans. Consideration will also be given to studies concerning the mutagenicity of known and expected metabolites.

8.1 GENE MUTATION TESTS

8.1.1 *Bacteria*

The ability of tetrachloroethylene to cause gene mutations in bacteria has been studied by several investigators. Many of these investigators used the Ames *Salmonella*/microsome test or modifications of that test. Different purities of tetrachloroethylene (stabilized* and low-stabilized materials) have been evaluated. (Bacterial studies are summarized in Table 8-2.)

Tetrachloroethylene is a volatile chemical, and thus, the standard Ames/*Salmonella* plate test, in which precautions are not taken to prevent escape of evaporated material, is not entirely suitable for its testing. Williams and Shimada (1983, sponsored by PPG Industries, Inc.), however, modified the standard plate procedure by exposing the bacteria to the test agent in a sealed chamber.

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*Stabilization is the intentional addition of material to increase the stability of tetrachloroethylene. Typically, the added stabilizers are acid and free radical scavengers (Dr. A. Philip Leber of PPG Industries, Inc., personal communication, September 1983).

TABLE 8-1. SUMMARY OF MUTAGENICITY TESTING OF TETRACHLOROETHYLENE

A. Gene Mutation Tests	Results[*]	References
Ames/*Salmonella* assay	+[**],-	Williams and Shimada 1983, Margard 1978, SRI International 1983, NTP 1983, Bartsch et al. 1979, Cerna and Kypenova 1977 (abstract)
Escherichia coli K12/343/113 ( ) Multi-purpose test	-	Henschler 1977, Greim et al. 1975
Saccharomyces cerevisiae D7 reverse mutation test (ivl-1 locus)	-	Callen et al. 1980, Bronzetti et al. 1983
Drosophila sex-linked recessive lethal test	-	Beliles et al. 1980
Host-mediated tests in mice: bacteria	wk	Beliles et al. 1980, Cerna and Kypenova 1977 (abstract)
yeast	-	Bronzetti et al. 1983
B. Chromosomal Aberration Tests		
Rat bone marrow assay	-[†]	Rampy et al. 1978, Beliles et al. 1980
Mouse bone marrow assay	-	Cerna and Kypenova 1977 (abstract)
Peripheral lymphocytes from exposed humans	-	Ikeda et al. 1980
Drosophila sex chromosome loss assay	-	Beliles et al. 1980
Rat dominant lethal assay	-	Beliles et al. 1980
C. Other Tests Indicative of DNA Damaging Activity		
Unscheduled DNA synthesis in WI-38	-[†]	Beliles et al. 1980
Hepatocyte primary culture/DNA repair test	+,-[††]	Williams and Shimada 1983, Williams 1983
Mitotic recombination tests in *Saccharomyces cerevisiae D7*	+,-	Callen et al. 1980, Bronzetti et al. 1983
D. DNA Binding Studies		
Whole mice	-	Schumann et al. 1980
E. Germ Cell Tests		
Altered sperm morphology	mouse + rat -	Beliles et al. 1980

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[*] + designates positive; - negative; wk weak response. Dose-response relationships were not established for the reported + results or wk results.

[**] Although increases several fold over background were observed, the positive results are considered weak because large amounts of material were needed to elicit the responses. Positive results were only obtained using airtight chambers (except for the study by Cerna and Kypenova 1977).

[†] Questionable evidence for weak or borderline activity in specific data sets.

[††] Positive results were found with vapor phase exposure and negative results were obtained using conventional phase exposure.

TABLE 8-2. RESULTS OF BACTERIAL TESTS OF DIFFERENT PURITIES AND SOURCES OF TETRACHLOROETHYLENE

Test system/strain	Purity/source	Concentrations tested	Metabolic activation	Protocol	Reported result	Reference
Ames/Salmonella TA98, TA100, TA1535	Perchlor 200-low-stabilized 99.93% purity PPG Industries, Inc.	1% v/v for TA98, TA1538, and TA1537; 0.1 1.0, 2.5, 5.0, 7.5, and 10% for TA100 and TA1535	Aroclor-induced rat S9 mix	Gas-phase exposure in airtight chambers	Positive at 2.5% (>97% toxicity) in base-pair substitution-sensitive strain (two to tenfold increases +/- M.A.*) dose-response not established	Williams and Shimada 1983
Ames/Salmonella TA98, TA100, TA1535 TA1537, TA1538	Perchlor 230-stabilized 99.80% purity PPG Industries, Inc.	1% v/v for TA98, TA1538, and TA1537; 0.1 1.0, 2.5, 5.0, 7.5, and 10% for TA100 and TA1535	Aroclor-induced rat S9 mix	Gas-phase exposure in airtight chambers	Positive at 2.5% (>97% toxicity) in base pair substitution sensitive strains (three to ten-fold increase +/- M.A.) dose-response not established	Williams and Shimada 1983
Ames/Salmonella TA100, TA1535	High purity Perchlor low-stabilized, 99.98+% purity, PPG Industries, Inc.	0.1, 1.0, and 2.5% v/v	Aroclor-induced rat S9 mix	Gas-phase exposure in airtight chambers	Negative	Williams and Shimada 1983

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*+/- M.A. designates response similar in the presence and absence of metabolic activation

(continued on the following page)

TABLE 8-2. (continued)

Test system/strain	Purity/source	Concentrations tested	Metabolic activation	Protocol	Reported result	Reference
Ames/Salmonella TA98, TA100, TA1535 TA1537, TA1538	Nonstabilized high purity Detrex Industries, Inc.	0.01, 0.05, and 0.1 ml/plate	Aroclor-induced rat S9 mix	Standard plate test in airtight chambers	Negative	Margard 1978
Ames/Salmonella TA98, TA100, TA1535 TA1537, TA1538	Stabilized 99.84% purity Detrex Industries, Inc.	0.01, 0.05, and 0.1 ml/plate	Aroclor-induced rat S9 mix	Standard plate test in airtight chambers	Positive (twofold increases in frameshift-sensitive strains and TA100) at 0.1 ml/plate (160 mg/plate). >90% toxicity. S9 mix increased response (10-to 17-fold increases)	Margard 1978
Ames/Salmonella TA98, TA100, TA1535 TA1537	99+% purity Aldrich	0.025, 0.05, 0.1, 0.5, 1.0 and 1.5 added to petri plate at bottom of desiccator	Aroclor-induced female and male rat liver S9 mix and Aroclor-induced female and male mouse liver S9 mix	Gas-phase exposure in airtight chambers	Negative	SRI International 1983
Ames/Salmonella TA98, TA100, TA1535 TA1537	Technical grade Fisher	3, 10, 33, 100, 333 ug/plate	Aroclor-induced rat liver S9 mix Aroclor-induced hamster liver S9 mix	Preincubation assay 10 min. 37°C	Negative	NTP 1983

(continued on the following page)

TABLE 8-2. (continued)

Test system/strain	Purity/source	Concentrations tested	Metabolic activation	Protocol	Reported result	Reference
Ames/*Salmonella* TA100	99.7% purity Merck-Darmstadt	0 to 663 mg/plate ($4x10^{-3}$M)	Phenobarbital-induced mouse liver microsomes with and without cofactors	Standard plate test	Negative	Bartsch et al. 1979
Ames/*Salmonella* tester strains not reported	Not reported	Not reported		Spot test	Positive	Cerna and Kypenova (1977, abstract)
E. coli K12/343/113 (>)	analytical grade Merck-Darmstadt	0.9 mM	Phenobarbital-induced mouse liver microsomes	Liquid suspension 2 hours at 37°C	Negative	Greim et al. 1975
Host-mediated assay ICR mice/*Salmonella* TA1950, TA1951, TA1952	Not reported	Not reported	Female mice	Not reported	Positive (mortality not reported)	Cerna and Kypenova (1977, abstract)
Host-mediated assay male and female CD mice/*Salmonella* TA98	91.43% purity North Strong Division Chemicals	Inhalation at 100 ppm and 500 ppm for 5 consecutive days	Male and female mice	Bacteria injected intraperitoneally after last exposure and removed 3 hours	Positive (twofold increases in revertants from 100 ppm in males; and fourfold increases in revertants from 500 ppm females).	Beliles et al. 1980

In their procedure, a known volume of test chemical was added to a glass petri plate containing a magnetic bar to ensure continuous stirring for even dissipation of vapors. The chamber was initially incubated at room temperature for 20 minutes, and then exposure was continued at 37°C for 18 hours, after which the bacterial test plates were removed from the chamber, covered with lids, and incubated another 30-54 hours at 37°C.

In the Williams and Shimada (1983) study, three types of material (provided by PPG Industries, Inc.) were tested in the presence and absence of S9 mix (derived from livers of Aroclor-induced rats): Perchlor 200 (low-stabilized, 99.93% purity), high purity Perchlor (low-stabilized, 99.98+% purity), and Perchlor 230 (stabilized, 99.80% purity).* Perchlor 200 and Perchlor 230 were evaluated in tester strains TA98, TA1537, and TA1538 at 1% (v/v) and in tester strains TA100 and TA1535 at 0.1, 1.0, 2.5, 5.0, 7.5, and 10% (v/v). High-purity Perchlor was evaluated in TA100 and TA1535 at 0.1, 1.0, and 2.5% (v/v). These concentrations represent the predicted concentration of the compound in the gas phase based upon calculations that consider the chamber volume and absolute temperature of the chamber, atmospheric pressure, and density of the test compound. (For example, 0.06, 0.62, 1.55, 3.1, 4.65, and 6.2 ml of tetrachloroethylene was added to the chamber for a 0.1, 1.0, 2.5, 5.0, 7.5, and 5% v/v vapor target concentration, respectively.) Positive responses were obtained for Perchlor 200 and 230 at 2.5% v/v (or 1.55 ml per desiccator) but not for high-purity Perchlor at the concentrations tested. A slightly higher response was observed with stabilized material. Positive results were repeated in a second experiment and were similar in the presence or absence of S9 mix. For example, in the absence of S9 mix Perchlor 200 (at 2.5%) increased the number of revertant colonies in the base-pair substitution-sensitive strains TA1535 (six to tenfold increases) and TA100 (two to threefold increases); Perchlor 230 (at 2.5% v/v) also caused increases in revertant numbers in TA1535 (approximately tenfold increases) and TA100 (approximately threefold increases). (See Figure 8-1 for an illustration of these responses). Negative results were found in frameshift-sensitive strains (TA98 and TA1538) for both Perchlor 200 and 230 in the presence or absence of S9 mix. At the next highest concentration (5% v/v) the revertant counts decreased to zero as toxicity became an important factor in the tests. The authors also indicated the test materials were toxic (> 97% killing) at the concentration (i.e., 2.5% v/v) that induced the mutagenic responses as determined by a simultaneous cytotoxicity test. Although the test materials may be quite toxic at 2.5% v/v, the investigator's method of quantifying cytotoxicity may not be accurate because the cell density that was used on each plate for the determination of toxicity is several orders of magnitude lower than that used for determination of mutagenicity (i.e., 10^7-10^9 cells). Nevertheless, it should be noted that because of toxicity, the mutagenic responses observed for Perchlor 200 and 230 are within a narrow range of concentrations. Because of this narrow range of effective concentrations and the concentration increments tested, a clear dose-response was not demonstrated.

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*Perchlor 200 contained 0.012 (% by weight) of hydroquinone monomethyl ether (HQMME) which provides minimal stabilization; Perchlor 230 contained 0.011% HQMME, 0.07% cyclohexene oxide, and 0.05% B-ethoxy propionitrile; high-purity Perchlor contained 0.01% HQMME (written communication from Dr. A. Philip Leber of PPG Industries, Inc., 1983).

In the Williams and Shimada (1983) study, high-purity material did not produce a detectable response under experimental conditions, as did the lower-purity materials (i.e., Perchlor 200 and 230). Therefore, the increases in revertants observed may be due to a contaminant(s). However, the high-purity Perchlor appeared to be more toxic (zero revertants observed at 2.5%) than the other test materials, and it is possible that a weak mutagenic response may have been masked by its toxicity. A weak response was observed for high-purity material at 1% in TA1535 (with S9 mix), but was not repeatable. Also, it should be pointed out that concurrent negative and positive controls were not used in this study. This weakens the negative conclusions for the high-purity material and makes interpretation of the magnitude of the responses in the presence of S9 mix for the lower-purity materials difficult.

Margard (1978) examined tetrachloroethylene (provided by Detrex Chemical Industries, Inc.) in the Ames/Salmonella test to determine whether mutagenic activity of technical grade samples is the result of added stabilizers. Precautions to prevent escape of material were taken (Margard, personal communication 1981), but they were not specified in writing. Tester strains TA1535, TA1537, TA1538, TA98, and TA100 were used. Tests were conducted in

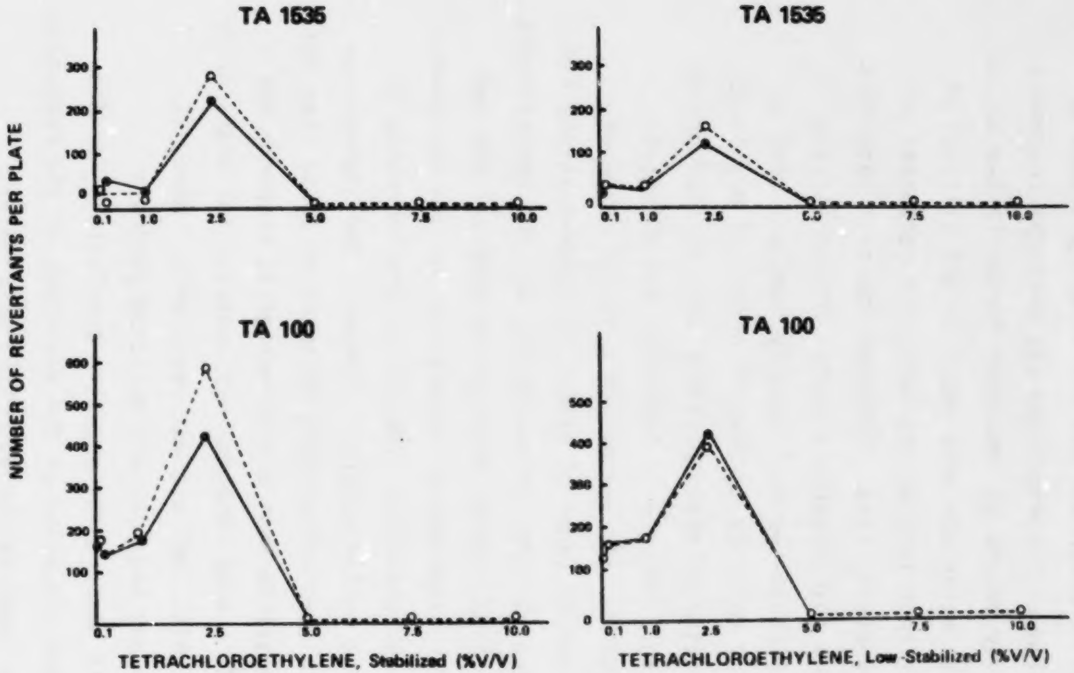

Figure 8-1. Dose-response curves for Perchlor 200 (low-stabilized tetrachloroethylene) and Perchlor 230 (stabiliz tetrachloroethylene) using Salmonella typhimurium tester strains TA100 and TA1535 in the presence of (○---○) and in the absence of (●—●) S9 mix (150 ul of Aroclor-induced rat liver). Each data point represents the geometric mean of triplicate plates from one experiment. (Williams and Shimada 1983)

the presence and absence of S9 mix (prepared from livers of Aroclor-1254 induced rats). Nonstabilized and stabilized materials were added directly to the petri plates at 0.01, 0.05, and 0.1 ml per plate rather than vapor exposure. The nonstabilized test material was described as purified tetrachloroethylene that contained no detectable epoxides or other stabilizing components, and the stabilized material was identified as an industrial degreasing grade of tetrachloroethylene that contained 0.07% (by weight) epichlorohydrin, 0.007% N-methylmorpholine, 0.07% beta-hydroxypronitrile, and 0.01% hydroquinone monoethyl ether (written communication from L. Schlossberg, Detrex Chemical Industries Inc., 1981). Nonstabilized test material was not detected as positive in the presence or absence of S9 mix. But stabilized material at 0.1 ml per plate (equivalent to 160 mg*) caused a weak response in the absence of S9 mix; twofold increases were observed for TA1538, TA98, and TA100. In the presence of S9 mix, greater increases in the number of revertants for tester strains TA1538 (17-fold increase), TA98 (10-fold increase), and TA100 (1.7-fold increase) at 0.1 ml per plate, were found. A clear dose-response was not observed for any of the tester strains. The toxicity of the test material was reported as greater than 90% killing at concentrations which caused increases in the number of revertants. The method used to determine toxicity may be inaccurate, as discussed previously for the Shimada and Williams study (1983). Negative results were reported for stabilized material in TA1535 and TA1537. Although the stabilized test material contained epichlorohydrin, which has been shown to be strongly mutagenic in Salmonella, it is primarily active in base-pair substitution-sensitive strains (i.e., TA1535 and TA100; McCann et al. 1975, Anderson et al. 1978), and thus it does not seem likely that this agent can solely account for the activity observed for stabilized material in the frameshift-sensitive strains TA1538 and TA98. Nevertheless, it appears that the mutagenic activity is due to the presence of a contaminant(s).

Other investigators have conducted studies in which precautions were taken to prevent escape of test material during testing. SRI International (1983 EPA-sponsored test) reported tetrachloroethylene (99+% purity,

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*Calculation based on the density of tetrachloroethylene as 1.586 g/ml.

Aldrich) to be negative when tested as a vapor in sealed desiccators using TA1535, TA1537, TA98, and TA100 with or without S9 mix prepared from livers of female and male Aroclor-1254 induced rats and mice. Cells were exposed at 37°C for 8 hours in desiccators, and then incubated at 37°C for an additional 42 hours. The concentrations tested were 0.05, 0.1, 0.5, 1.0, 1.5 ml added to a petri plate at the bottom of the desiccator chamber in one experiment and 0.025, 0.05, 0.1, 0.5, and 1.0 ml added to a plate at the bottom of the desiccator in another experiment. A toxic response (reduction or absence of bacterial lawn) was found at 1.5 ml/per desiccator.

The National Toxicology Program (NTP 1983) sponsored Salmonella testing on tetrachloroethylene (technical grade, source Fischer) and obtained negative results. Four standard tester strains were used: TA98, TA100, TA1535, and TA1537. A preincubation protocol was followed in which the cells, S9 activation system, and chemical are preincubated in test tubes for 20 minutes at 37°C before addition of the top agar and plating in petri plates. Two different S9 systems were used; S9 mix derived from livers of Aroclor-1254 induced rat liver and Aroclor-1254 induced hamster liver. Tests were also conducted in the absence of S9 mix. Six concentrations (0, 3, 10, 33, 100, 333 ug/plate) were evaluated. (In TA100, up to 10,000 ug/plate was evaluated.) Although incubation was carried out in capped tubes, it is possible that evaporation and some escape may have occurred. However, it should be noted that toxic levels were tested as indicated by absence or reduction of bacterial lawn.

Bartsch et al. (1979) investigated the mutagenicity of tetrachloroethylene (99.7% purity, Merck-Darmstadt) using the standard Ames/Salmonella plate test in which precautions to prevent escape of test material are not taken. Negative results were obtained using tester strain TA100 in the presence of mouse liver microsomes with and without cofactors. The authors indicated that toxic concentrations (above 82.9 mg/plate) were tested, but did not indicate their criteria for determining toxicity. Interpretation of these negative conclusions is limited by the amount of data presented and because only one tester strain was evaluated.

In an abstract, Cerna and Kypenova (1977) reported that in a spot test protocol of the Ames/Salmonella assay, tetrachloroethylene (purity and source not reported) induced both base-pair substitution and frameshift mutations in Salmonella typhimurium. The results were obtained in the absence of exogenous activation. These authors also reported that in a host-mediated assay using female ICR mice, tetrachloroethylene induced significant increases in the number of revertants in tester strains TA1950, TA1951, and TA1952 at dosage levels reported as representing the LD_{50} and one-half of the LD_{50}. These results were reported as not being dose-dependent. Because this report was in abstract form and did not provide details of the protocol nor present the data, the acceptability of the test results is indeterminate. Also, the possibility of mutagenic contaminants must be considered.

Beliles et al. (1980) used a host-mediated assay to evaluate the effects of tetrachloroethylene (91.43% pure from North Strong Division Chemicals) in the presence of whole mammal metabolism. In this study, Salmonella tester strain TA98 was used as the indicator organism, and male and female mice (strain CD-1) were the hosts. The animals were exposed by inhalation 7 hours per day for 5 days to either 100 ppm or 500 ppm. Bacteria were injected intraperitoneally into the mice after the last exposure. The bacteria were removed from the mice 3 hours later. At the 100 ppm dose level, increases in the number of revertants were observed for males (approximately twofold increase) but not for females. At 500 ppm, a positive response was reported for females (approximately fourfold increase) but not for males. Because of the lack of a dose-response and the weak responses, these findings should be viewed with caution. Also, the material used was of low-purity, and the responses may have been due to contaminants and/or added stabilizers. In addition, parallel in vitro plate tests using Salmonella were not conducted. The parallel plate tests are important the determination of the requirement of whole-mammal activation.

Studies on tetrachloroethylene have also been conducted in Escherichia coli. Henschler (1977) reported that tetrachloroethylene was not mutagenic when tested in E. coli K12 with metabolic activation (liver microsomal fraction prepared from phenobarbital-induced mice). This report, however, is difficult to evaluate because actual revertant count data (experimental and control number of revertants) and the details of the protocol are not provided. It appears that the conclusions presented in this report are actually based on data derived from the study by Greim et al. (1975).

Greim et al. (1975) reported that negative results were obtained when tetrachloroethylene (purity reported as analytical grade; Merck-Darmstadt) was assayed in the multi-purpose test system of Escherichia coli K12/343/113 (>). Tests were conducted in the absence and presence of metabolic activation (phenobarbital-induced mouse liver microsomal fraction plus NADPH cofactors) at a concentration of 0.9 mM and a treatment time of 2 hours in liquid suspension at 37°C. These treatment conditions resulted in 99 + 1% survival. The genetic markers evaluated for mutation induction were the missense marker arg+ and the frameshift marker nad+ for reverse mutation, and gal+ and MTR for forward mutation. Deficiencies in the study design and reporting of the results reduce the weight of the negative conclusion. These deficiencies are as follows: 1) only one concentration was evaluated, 2) adequate exposure may not have been achieved, as indicated by the high survival, 3) there was no reporting of revertant count data (experimental and control), and 4) there was no reporting of the number of replicate plates used or the number of the tests conducted.

The bacterial tests discussed above do not clearly demonstrate that tetrachloroethylene itself is mutagenic. The positive responses found may be due to contaminants and/or added stabilizers. The induced increases in revertants did not require exogenous metabolic activation and were observed in both frameshift and base-pair substitution-sensitive tester strains. The positive findings were not considered strong in that large amounts of material (estimated vapors at 2.5% v/v and at 160 mg/plate) were needed for the detection of mutagenicity. Also, there was a very narrow range of effective concentrations because of toxicity; thus dose-response relationships were not established. When tested, highly purifed samples were not detected as mutagenic under the conditions in which technical samples caused increases in the number of revertants. Although some technical tetrachloroethylene samples were positive, there were other samples that were not detected as positive. The available results provide suggestive evidence that certain technical samples of tetrachloroethylene are weakly mutagenic in Salmonella and that the positive responses may be due to impurites and/or added stabilizers.

8.1.2 Drosophila

Beliles et al. (1980) used the sex-linked recessive lethal assay in Drosophila melanogaster to test tetrachloroethylene (91.43% purity, North Strong Division Chemicals) and reported negative results. Adult male flies were exposed for 7 hours by inhalation at 100 ppm and 500 ppm. Treated males were

mated to nontreated females at various times (2-3-3-2 day mating scheme) to test specific germ cell stages. No significant increases ($P < 0.05$) over the background values were observed. However, only a small sample size was examined. A total of 3804 chromosomes for the 100 ppm dose and 3956 chromosomes for the 500 ppm dose were evaluated. This sample size was only large enough to exclude the induction of an approximately fourfold increase in mutation frequency (Kastenbaum and Bowman 1970). Ideally, at least 7000 chromosomes at each dose level should be screened to preclude a doubling in mutation frequency, which is generally considered to be the increase of biological significance. Survival was not reported in this study, and thus it is uncertain whether a sufficient dose was given. These deficiencies prevent a judgment regarding the mutagenic activity of tetrachloroethylene in Drosophila.

The ability of tetrachloroethylene to cause gene mutations in an eucaryotic organism has not been adequately examined. The only available study was a sex-linked recessive lethal test in Drosophila in which tetrachloroethylene was not properly evaluated.

8.2 CHROMOSOMAL ABERRATION TESTS

8.2.1 Whole-Mammal Bone Marrow Cells

Rampy et al. (1978) examined bone marrow cells for chromosome aberrations from male and female Sprague-Dawley rats after tetrachloroethylene exposure. Animals were exposed to 300 ppm (2.03 mg/l) or 600 ppm (4.07 mg/l) tetrachloroethylene* by inhalation 6 hours/day, 5 days/week, for one year. Three animals per dose were examined. The authors reported "zero" chromosomal aberrations per cell for both females and males. The data for females, however, are inadequate for a clear interpretation because of the very low number of metaphases scored (less than 25 cells per animal). In male rats, 150 cells were scored (50 cells per animal). The negative controls were also reported as "zero" aberrations. This observation is very unusual because, in general, most laboratories have reported about 1 to 2% total aberrations for background values. In this study, it is not known whether the highest exposure level was near the maximum tolerated dose (MTD) for females because no weight loss and no mortality was observed. In males there was no weight loss, but significant increases in mortality above control values were observed at the highest dose tested, and therefore an MTD may have been approached. It is not apparent that the investigators determined the toxicity of the test material to arrive at an MTD for this study, because the dosage levels used were based on the threshold limit value of 100 ppm for tetrachloroethylene.

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*Formulation (liquid volume percent): trichloroethylene, 3 ppm; hexachloroethane, < 12 ppm; carbon tetrachloride, 2 ppm; 4-methyl morpholine, 44 ppm; nonvolatile residue, 2 ppm; and tetrachloroethylene balance.

A rat bone marrow assay was also performed by Beliles et al. (1980) and reported as negative. Ten males and ten females [CRL:COBS CD(SD)BR] were exposed to an acute dose of 100 ppm and 500 ppm tetrachloroethylene (91.43% purity, North Strong Division Chemicals) by inhalation for 7 hours. Bone marrow cells were harvested 6, 24, and 48 hours later. No increase in aberrations was found for females, but for males, weak clastogenic effects (breaks, fragments, deletions, and aneuploid cells) were observed. At 500 ppm, 3.3% cells with aberrations versus 0.7% in the control were found at the 24-hour kill. A subchronic study (five exposures, 7 hours per day) at 100 ppm and 500 ppm was also conducted. Animals were killed 6 hours after the last exposure. No increase in abnormalities was found in males, and only a slight increase at 100 ppm (1% cells with aberrations) was found in females. This response was not dose-related. The female subchronic control group had a very low background (0.3% cells with aberrations). Although isolated incidences of increases in chromosomal aberrations were observed, the lack of dose-responses precludes an unequivocal positive conclusion. On the other hand, a negative conclusion cannot be drawn because the authors did not discuss the criteria used to select the dosage levels, and thus, there is the possibility that a toxic dose may not have been evaluated.

Cerna and Kypenova (1977) reported in an abstract that mice (ICR) given an acute intraperitoneal dose one half of the LD_{50} of tetrachloroethylene or dosed intraperitoneally for five applications in 24 hour intervals (dose of one injection equalled 1/6 LD_{50}) did not show cytogenetic effects in the bone marrow cells. Details of the protocol and the cytogenetic data were not available for an evaluation. Hence, the negative conclusion of the authors cannot be considered definitive.

8.2.2 Human Peripheral Lymphocytes

Ikeda et al. (1980) studied chromosomal aberrations, sister chromatid exchanges (SCEs), and variation in the mitotic index of peripheral lymphocytes cultured from ten workers (seven males and three females) occupationally exposed to technical grade tetrachloroethylene (impurities not reported). The workers were divided into high (Group 1) and low (Group 2) exposure groups. Group 1 consisted of six workers (five males and one female aged 20 to 66 years) from a degreasing workshop.

These workers had a geometric mean exposure of 92 ppm (range 30 to 220 ppm). The five males of Group 1 had work histories of 10 to 18 years, whereas the one female had worked in the degreasing shop for only 1 year. Group 2 included four workers (two males and two females aged 17 to 31 years) from a support department with a shorter work history (3 months to 3 years) and with an exposure range of 10 to 40 ppm. The control group consisted of six males and five females. The authors did not indicate if this was a matched control, and did not indicate the medical histories of the subjects (e.g., recent illnesses, radiation exposures). There were no statistically significant differences ($P > 0.05$) in the incidences of chromosomal aberrations (structural and numerical) and SCEs between the exposed workers and control group. The mitotic index was similar for both exposed and control groups.

8.2.3 Drosophila

In addition to performing the sex-linked recessive lethal assay discussed earlier, Beliles et al. (1980) also conducted a sex chromosome loss assay on low-purity (91.4%, North Strong Division Chemicals) tetrachloroethylene for nondisjunction in *Drosophila melanogaster*. Males were exposed to 100 and 500 ppm of tetrachloroethylene for 7 hours. The phenotypic classes used allow for detection of losses of the entire X or Y chromosome and the short or long arm of the Y chromosome. Although marginal increases, which were not dose-related, were observed after tetrachloroethylene treatment, they are not considered sufficient to judge the data as positive or negative.

The cytogenetic tests discussed above using mice, rats, *Drosophila*, and exposed humans have been reported as negative. Although these studies are not considered to be a thorough evaluation of the ability of tetrachloroethylene to cause chromosomal aberrations, the data collectively indicates that tetrachloroethylene is not strongly clastogenic. However, there have been no adequate studies on the ability of tetrachloroethylene to cause chromosome nondisjunction (aneuploidy).

8.3 OTHER TESTS INDICATIVE OF DNA DAMAGE

8.3.1 DNA Repair

Unscheduled DNA synthesis (UDS) is measured by repair of DNA lesions, which is indicative of DNA damage. Beliles et al. (1980) assessed the ability of tetrachloroethylene (91.43% purity, North Strong Division Chemicals) to cause UDS in human fibroblast (WI-38) cells. Because WI-38 cells have little if any enzyme activation capability, the tests were conducted with an exogenous source of metabolic activation (i.e., S9 mix). The test material was examined at 0.01, 0.05, 0.1, and 0.5% (v/v) using conventional liquid phase exposure. Scheduled DNA synthesis was blocked by treatment with hydroxyurea, and UDS was measured by liquid scintillation counting of incorporated tritiated thymidine ([^{3}H]-TdR) into DNA. A very slight increase was seen at 0.01% (v/v) tetrachloroethylene both in the presence (1.5-fold of control) and absence (1.35-fold of control) of Aroclor rat liver S9 mix. No increases occurred at 0.1 and 0.5%. A toxic response was reported at 0.5% (i.e., a decrease in total amount of DNA as well as in the incorporation of [^{3}H]-TdR). An increase in total amount of DNA at 0.01% was found, suggesting that more cells are entering the S phase. Cells accelerated into S phase would account for the increases seen in [^{3}H]-TdR incorporation at 0.01%. Therefore, it is uncertain whether tetrachloroethylene induced a weak UDS response in this system. Also, other problems were found in this study. The positive controls gave weak responses. N-methyl-N'-nitro-N-nitrosoguanidine elicited a weak response (1.8-fold increase), but at a toxic concentration (5 ug/ml) as indicated by a decrease in total DNA (6.27 ug of DNA versus 23.76 ug of DNA in solvent control). Benzo[a]pyrene gave a response of 1.16-fold above background. This is an equivocal response, particularly because there was also an increase found in the total amount of DNA.

Williams and Shimada (1983, sponsored by PPG Industries, Inc.) evaluated two different samples of tetrachloroethylene, Perchlor 200 (low-stabilized, 99.93% purity) and Perchlor 230 (stabilized, purity 99.80%), for their ability to cause UDS in the hepatocyte primary culture (HPC)/DNA repair test. The target cells in this test system have a capability to metabolize xenobiotics. Williams and Shimada measured UDS by autoradiographic determination of the amount of [^{3}H]-TdR (10 uCi/ml) incorporated into nuclear DNA. Hepatocytes were isolated from adult male Fischer 344 rats. Cells were treated for 18 hours or 3 hours. For the 3-hour exposure, cultures were incubated another 15 hours in the absence of tetrachloroethylene to allow for DNA repair synthesis. The criterion that was used for a positive result was a net nuclear grain count of 5 in triplicate coverslips.* Negative results were reported for both Perchlor 230 (at concentrations of 0.001, 0.01, 0.1, and 1.0% v/v) and Perchlor 200 (at concentrations of 0.0001, 0.001, 0.1, and 1.0%) when tests were conducted using conventional liquid-phase exposure in which tetrachloroethylene was added to the culture medium.

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*Nuclear grain counts were reported as the mean ± standard deviation. Cytoplasmic grain counts in three nuclear size areas adjacent to the nucleus were determined. The highest cytoplasmic grain count was subtracted from the nuclear count. This value is referred to as "net" grain count.

For both materials, positive responses were reported when testing was performed using vapor-phase exposure in gas tight chambers. Testing was conducted at 0.1, 1.0, and 2.5% v/v (desired air concentration) for 3 and 18 hours. Perchlor 230 at 0.1% caused an increase in UDS when the cells were exposed for 3 hours (6.2 ± 4.9 net nuclear grain count, 50% cells showing toxic effects[†]) and for 18 hours (15.9 ± 1.6 net nuclear grain count, 25% cells showing toxic effects). Perchlor 200 caused an increase in UDS at 0.1% v/v for the 3-hour treatment (10.8 ± 6.1% net nuclear grain count, 75% cells showing toxic effects) but not for the 18-hour treatment. At 1.0% and 2.5% for both materials at both treatment times, nearly 100% of cells showed toxic effects. It should be pointed out that the background control values were taken from the conventional exposure experiment. This makes intrepretation of the results difficult, particularly because the conventional-phase media was different from the gas-phase media. Because these data are based on one test in which there were no concurrent positive and negative controls, the results are considered only suggestive of a positive effect. To validate these findings it is necessary to repeat experiments using appropriate concurrent controls and a concentration range to demonstrate a dose-response. Although the possibility exists that an impurity(ies) may be responsible for the observed effects, the authors did not examine high-purity Perchlor (99.98+%) as they did in the *Salmonella* tests discussed earlier. If high-purity material had tested negative under the same experimental conditions under which the lower-purity materials tested positive, as in the *Salmonella* test, a stronger argument could be made that impurities were causing the effects.

Williams (1983) conducted HPC/DNA repair tests using hepatocytes from male $B_6C_3F_1$ mice and male Osborne-Mendel rats on tetrachloroethylene (99+% purity, Aldrich Chemical Company). Conventional liquid-phase exposure conditions were used. Negative results were reported for both rat and mice hepatocytes when tetrachloroethylene was added to the culture medium at 0.00001, 0.0001,

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[†] Toxicity identified by the absence of S phase cells and general cellular morphology. This is not an accurate method of determining toxicity.

0.001, 0.01, and 0.1% (v/v) for 18 hours. The material was reported as "toxic" at 0.01% and higher. The highest cytoplasmic grain count was subtracted from the nuclear count. This reduces the possibility of false positives, but the chance of missing a weak UDS inducer would be increased, especially if the cytoplasmic grain count is high. This consideration also applies to the Williams and Shimada conventional-phase exposure study discussed previously. The cytoplasmic grain counts were not reported in any of the HPC/DNA repair studies.

8.3.2 Mitotic Recombination

Callen et al. (1980) evaluated the ability of tetrachloroethylene (purity not reported, stabilized 0.01% thymol, Eastman Kodak) to cause mitotic gene conversion (nonreciprocal recombination) at the trp-5 locus, mitotic crossing-over (reciprocal recombination) at the ade-2 locus, and gene mutation (reversion) at the ilv-1 locus in log phase cultures of *Saccharomyces cerevisiae* D7. Cells were incubated for one hour in culture medium containing 0, 4.9, 6.6, and 8.2 mM tetrachloroethylene. No exogenous source of metabolic activation was used in these studies. At 4.9 mM (84% survival), no significant increases in the frequency of gene conversion (1.9 convertants/10^5 survivors versus 1.4 convertants/10^5 survivors in background control) and mitotic crossing-over (5.3 mitotic recombinants/10^4 survivors versus 3.3 mitotic recombinants/10^4 survivors in background control) occurred. As shown in Figure 8-2, when the concentration of tetrachloroethylene was increased to 6.6 mM (58% survival), increases in mitotic gene conversion and mitotic crossing-over did occur (8.3 convertants/10^5 survivors and 52.6 mitotic recombinants/10^4 survivors, respectively). Mitotic recombinational activity was not determined at 8.2 mM because less than 0.1% survival was found. No significant increases in gene mutations were observed at 4.9 mM (3.8 revertants/10^6 survivors versus 2.9 revertants/10^6 survivors in control). The reverse mutation frequency was not determined at 6.6 mM. Therefore, the induced number of revertants is too low to be indicative of a positive result, but the high values for the recombinational events do indicate a positive effect at 4.9 mM test material. The possibility that the effects were caused by a mutagenic impurity(ies) should be considered. It should be pointed out that in the study by Callen et al. the Ade$^+$ recombinants were estimated from a total of 30 plates, ten of which contained minimum medium (plus adenine and isoleucine) used for estimating

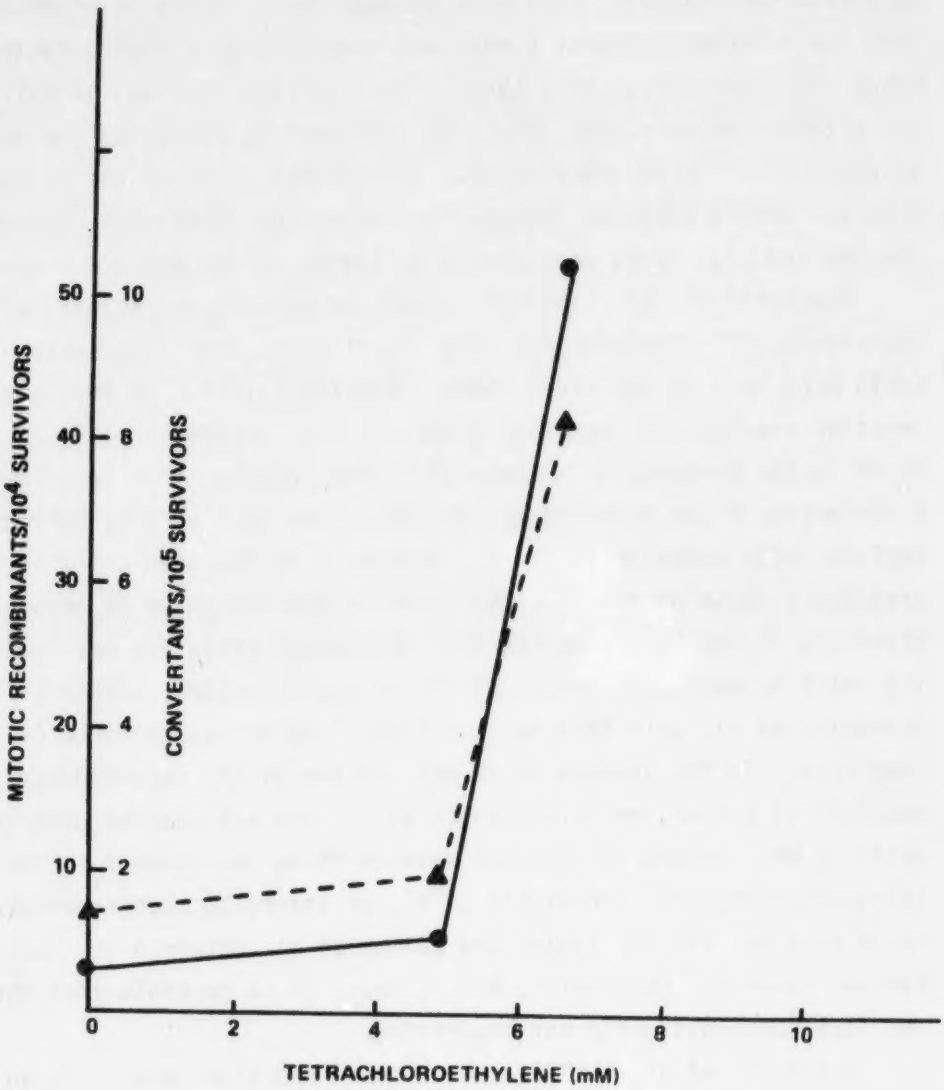

Figure 8-2. Induction of mitotic recombination by tetrachloroethylene in *Saccharomyces cerevisiae* D7. The frequency of mitotic crossing-over (●—●) and gene conversion (▲--▲) was determined. Log-phase yeast cells were treated with test chemical for one hour without the addition of an exogenous metabolic activation system. (Adapted from Callen et al. 1980)

the number of trp-5 convertants. Because mitotic crossing-over and gene conversion are not necessarily distinct events, in that they probably depend on a common inducible mechanism, the number of Ade$^+$ recombinants may have been overestimated by including those Ade$^+$ that were already Trp$^+$. There is experimental support that these recombinational events are inducible by a common factor(s) (see Fabre Fabre and Roman 1977, Fabre 1978). The positive findings of Callen and coworkers for mitotic recombination should be confirmed by repeating the assay using appropriate selection conditions. In addition, because the responses were observed within a narrow "window," at least one additional concentration between the low and high doses used should be tested to demonstrate a clear dose-response.

Bronzetti et al. (1983) also used the yeast *S. cerevisiae* D7 to evaluate the effects of tetrachloroethylene (99.5% pure, stabilized with 0.01% thymol, Carlo Erba Co.) at the trp-5, ade-2, and ilv-1 loci. In this study, however, negative results were obtained after a 2-hour treatment at 5, 10, 20, 60, and 85 mM in the presence or absence of S9 mix (Aroclor-1254 induced rat liver). Differences in the experimental protocol from that used by Callen et al. may explain these negative findings. Bronzetti et al. used cells in the stationary phase of growth rather than in the log phase of growth. For some chemicals it has been observed that stationary cells are more refractory than log cells to mutagenic treatment (Mayer and Goin 1980, Shahin 1975). Bronzetti et al. were able to test higher concentrations than Callen and coworkers. In the absence of S9 mix, Callen et al. reported less than 0.1% survival at 8.2 mM, while Bronzetti et al. did not observe complete killing until 85 mM. Another difference between these two studies is the source of tetrachloroethylene. Bronzetti et al. purchased tetrachloroethylene from Carlo Erba Co. (Milan, Italy) and Callen et al. obtained the test agent from Eastman Kodak Co. (Rochester, N.Y.); thus, it is possible that the test samples may have contained different impurities.

Bronzetti et al. (1983) also obtained negative results in an intrasanguineous host-mediated assay using *S. cerevisiae* D7 as the indicator organism and CD-1 mice as the host. Stationary yeast cells (4 x 10^8 cells) were injected into the retro-orbital sinus of mice. After injection of the yeast, an acute oral dose of 11 g tetrachloroethylene/kg body weight (b.w.) was given. A subacute dose of 2 g/kg b.w. given 5 days a week for a total of 12 administrations was also used (the last test dose was 4 g/kg b.w.; therefore, the total dose was 26 g/kg b.w.). In the subacute study, yeast cells were injected after the last dose of tetrachloroethylene (i.e., 4 g/kg b.w.). Four hours after injection of yeast, in both the acute and subchronic study, the cells were recovered from the liver, lungs, and kidneys of three animals. No concurrent positive control chemical was used in these studies to ensure that the system was functioning properly.

The positive responses discussed above for mitotic recombination in yeast and DNA repair synthesis in mammalian cells provide suggestive evidence that certain technical samples of tetrachloroethylene may be active in damaging DNA. However, toxic concentrations of material were needed to elicit these responses. The possibility that impurities and/or added stabilizers caused the increased effects should be considered.

8.4 DNA BINDING STUDIES

Chemical adduct formation is a critical step in certain types of mutagenesis. Schumann et al. (1980) reported that there was no detectable binding of ^{14}C-labeled tetrachloroethylene (99% purity) to DNA when mice were treated by inhalation at 600 ppm for 6 hours or when they were given an acute dose of 500 mg/kg orally. The specific activity of the ^{14}C-label (26,593 dpm/umol in the inhalation study and 133,273 dpm/umol in the oral study) is too low, however, to preclude the possibility of very low levels of DNA binding. For example, at the specific activities used under the experimental conditions, at an assumed binding level of 10^{-5} alkylations per nucleotide (Stott and Watanabe 1982) there would be 5-10 dpm per sample. This is at the limit of practical detection. Therefore, the possibility of binding at slightly less than 10^{-5} alkylations per nucleotide cannot ruled out. These negative findings, however, are consistent with the negative and weak results reported in the mutagenicity tests discussed above.

8.5 STUDIES INDICATIVE OF MUTAGENICITY IN GERM CELLS

An important aspect of a mutagenicity evaluation is to assess the potential of the chemical to reach the germinal tissue of humans and cause mutations that may contribute to the genetic disease burden. This assessment is almost always based on animal experimentation. The ability of tetrachloroethylene to cause genetic damage in germinal tissue has not been well studied. The only test results available were from a dominant lethal study in rats [CRL: COBS CD(SD)BR] and a sperm morphology assay in both rats and mice (strain CD-1). Tetrachloroethylene (91.43% purity, North Strong Division Chemicals) did not cause an increase in dominant lethals in rats when unexposed females were mated during a 7-week period to exposed adult males given an acute dose of 100 ppm and 500 ppm by inhalation for 7 hours per day for 5 days (Beliles et al. 1980). The dominant lethal assay is generally thought to measure gross chromosome damage (Bateman and Epstein 1971). Also, this test is not considered a sensitive assay because of the high spontaneous level of lethal events (Russell and Matter 1980), and thus, negative results do not necessarily indicate that the chemical does not reach and damage the germ cell DNA.

Beliles et al. (1980) also examined tetrachloroethylene for altered sperm morphology in treated rats and mice. After dosing at 100 ppm and 500 ppm by inhalation 7 hours per day for 5 consecutive days, groups of four animals were killed at the end of 1 week, 4 weeks, and 10 weeks to examine effects on various germ cell stages. Sperm was collected from the cauda epididymis, and at least 500 cells were examined. Negative results were reported in rats; the mice, however, showed positive responses. At 500 ppm, 19.7% abnormal sperm were observed (versus 6.0% in the negative controls) during the fourth week after exposure (corresponding to the spermatocyte stage). By themselves, these positive findings alone are not sufficient to conclude that tetrachloroethylene alters germ cell DNA because this assay is only an indicator of chemical effects on sperm and does not provide definitive evidence that a chemical reached germinal tissue and damaged DNA. Therefore, because limited information was provided, it is not clear whether tetrachloroethylene (or impurities) reaches the germ tissue. However, if tetrachloroethylene reached germ cell DNA, there may be no serious risk of mutation because of the largely negative or marginal results found in mutagenicity tests discussed previously.

8.6 MUTAGENICITY OF METABOLITES

Trichloroacetic acid (TCA) is a known human metabolite of tetrachloroethylene. The formation of TCA is thought to occur through the formation of an epoxide, tetrachloroethylene oxide, and its subsequent rearrangement to trichloroacetyl chloride or trichloroacetaldehyde, which then rapidly hydrolyzes to TCA. (See chapter 5 on metabolism for a more detailed discussion.) These intermediates are considered relevant in assessing the mutagenicity of tetrachloroethylene.

Tetrachloroethylene oxide, which is considered to be the biologically active intermediate of the parent compound tetrachloroethylene, was assayed for mutagenicity in the absence of exogenous metabolic activation in several bacterial tests (Kline et al. 1982). Tetrachloroethylene oxide increased the number of revertants in a dose-dependent manner in Salmonella tester strain TA1535 when assayed by a preincubation liquid protocol (20 minutes at 37°C), but did not cause an increase in revertants using Escherichia coli WP2 uvr A. In Salmonella, a 14-fold increase occurred at 2.5 mM and a 20-fold increase occurred at 5mM. Tetrachloroethylene epoxide was toxic at 25mM.

This epoxide was also evaluated by Kline et al. (1982) in the E. coli pol A assay. Positive effects were observed at 0.04, 0.09, and 0.44 mM/ml as measured by differential growth inhibition of a DNA polymerase-deficient strain in comparison with its polymerase-proficient parent.

Waskell (1978) tested TCA at 0.45 mg/plate in Salmonella TA98 and TA100 and obtained negative results. There are other intermediates which have not been identified in humans but are thought to occur (e.g., trichloroethanol chloral hydrate). Waskell (1978) obtained negative results for trichloroethanol in Salmonella TA98 and TA100 up to a dose of 7.5 mg/plate. Gu et al. (1981), however, reported suggestive evidence that trichloroethanol weakly induced sister chromatid exchange (SCE) formation in primary cultures of human lymphocytes.

Chloral hydrate was reported to be marginally mutagenic (less than twofold increase over a dose range of 0.5 to 10 mg per plate) in Salmonella TA100 (Waskell 1978). Gu et al. (1981) also provided suggestive evidence than chloral hydrate at 54.1 mg/l caused a weak increase in SCEs in cultured human lymphocytes. Chloral hydrate has also been shown to block spindle elongation in insect spermatocytes (Ris 1949). Data on metabolites of tetrachloroethylene suggest that if the parent compound was biotransformed, its metabolites may be genotoxic; these data are limited, however, and additional studies are needed on metabolism and on the mutagenicity of metabolites to reach a clear conclusion.

8.7 SUMMARY AND CONCLUSIONS

Tetrachloroethylene itself has not been clearly shown to be a mutagen. Certain commercial and technical preparations have elicited positive responses in the Ames bacterial test, a yeast recombinogenic assay, a host-mediated assay using *Salmonella*, and DNA repair assays. In general, the responses were weak, and eliciting them required rather high toxic concentrations of tetrachloroethylene. No dose-response relationships were established in these studies. The positive findings may be explained by the presence of mutagenic contaminants and/or added stabilizers. Highly purified tetrachloroethylene has only been evaluated in the Ames/*Salmonella* test, where negative results were obtained.

Several other tests of commercial and technical samples have been reported to be negative. In addition, The National Toxicology Program (NTP) has recently sponsored mutagenicity testing (a modified Ames *Salmonella* test, a sex-linked recessive lethal test in *Drosophila*, sister chromatid exchange formation and chromosome aberrations in Chinese hamster ovary cells *in vitro* on a technical sample of tetrachloroethylene; the preliminary results were negative. (These studies are in the process of being peer-reviewed, and were not discussed in this chapter, except for the Ames test.) The inconsistencies of available results on different samples of tetrachloroethylene may be a function of the toxicity of the test material, of exposure conditions used for testing this volatile chemical, or of differences in sample contaminants and/or added stabilizers. Information on chemical composition of the tetrachloroethylene test samples was scarce.

Although tetrachloroethylene itself has not been shown to be mutagenic, it should be emphasized that the negative results are not wholly unequivocal. Appropriate concurrent controls, adequate sample sizes, and exposure conditions were sometimes not used, and in some cases the available data are not sufficient to determine whether an adequate test was conducted. Also, there have been no reliable studies investigating the ability of tetrachloroethylene to cause chromosome nondisjunction, which would result in aneuploidy, a significant genotoxic effect.

Because the epoxide of tetrachloroethylene was mutagenic in bacterial studies, the concern should be raised that it may pose a mutagenic hazard. It should be noted, however, that the parent compound was assayed in the presence of several types of metabolic activation systems (i.e., liver homogenates, intact hepatocytes, and whole mammals) and the results were largely negative or weakly positive. Therefore, it is uncertain whether these negative or weak findings were the result of limitations of the activation systems, the epoxide not being produced in sufficient quantities, or the epoxide possessing too short a half life to cause a detectable mutagenic response.

In conclusion, inadequate information exists to warrant a provisional classification of tetrachloroethylene either as nonmutagenic or mutagenic. If tetrachloroethylene is a mutagen, the evidence available thus far indicates that it is only weakly so. (Because of insufficient information, this conclusion is not made with regard to its potential for causing chromosome nondisjunction.) Certain commercial and technical preparations of tetrachloroethylene may contain mutagenic impurities and/or added stabilizers. Although there may be mutagenic agents in certain preparations of tetrachloroethylene, usually large amounts of material (at toxic levels) were required to elicit weak responses.

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9.0 CARCINOGENICITY

The purpose of this section is to provide an evaluation of the likelihood that tetrachloroethylene (perchloroethylene) is a human carcinogen and, on the assumption that it is a human carcinogen, to provide a basis for estimating its public health impact, including a potency evaluation, in relation to other carcinogens. The evaluation of carcinogenicity depends heavily on animal bioassays and epidemiologic evidence. However, information on mutagenicity and metabolism, particularly in relation to interaction with DNA, as well as to pharmacokinetic behavior, has an important bearing on both the qualitative and quantitative assessment of carcinogenicity. The available information on these subjects is reviewed in other sections of this document. This section presents an evaluation of the animal bioassays, the human epidemiologic evidence, the quantitative aspects of assessment, and finally, a summary and conclusions dealing with all of the relevant aspects of the carcinogenicity of tetrachloroethylene.

9.1 ANIMAL STUDIES

Two long-term animal bioassays have been performed to assess the carcinogenic potential of tetrachloroethylene. In one study involving exposure of rats and mice to tetrachloroethylene by gavage, the National Cancer Institute (NCI) (1977a) reported the induction of hepatocellular carcinomas in male and female mice, but determined that the test with rats was inconclusive because of excessive mortality. In the other study, in which Sprague-Dawley rats were exposed to tetrachloroethylene by inhalation, the Dow Chemical Company (Rampy et al. 1978) reported no evidence for the carcinogenicity of the chemical. However, limitations in this study make it difficult to assess the carcinogenic potential of tetrachloroethylene.

9.1.1 National Cancer Institute Bioassay (1977a)

The tetrachloroethylene sample used in this bioassay was purchased from the Aldrich Chemical Company, Milwaukee, Wisconsin. Analysis by gas-liquid chromatography and infrared spectroscopy yielded results indicating a purity of > 99% with at least one minor impurity not identified in the report. Identification of the impurities in the test sample was not made (personal communications with the NCI and the Aldrich Chemical Company).

The carcinogenicity of tetrachloroethylene was tested in Osborne-Mendel rats and B6C3F1 mice. The initial age of the weanling animals was 25 days for the mice and 35 days for the rats. Two treatment groups consisted of 50 males and 50 females, and matched vehicle (corn oil) and untreated control groups comprised 20 animals of each sex. Selected dosage levels were those determined to be maximally tolerated in an 8-week subchronic study, i.e., a dosage that was not fatal and/or did not reduce body weight gain more than approximately 20%, and one-half maximally tolerated in an 8-week subchronic toxicity test. Time-weighted average doses (mg/kg/dose) in the chronic study were 941 and 471 for male rats, 949 and 474 for female rats, 1,072 and 536 for male mice, and 772 and 386 for female mice. Tetrachloroethylene was administered to the animals by gastric intubation in corn oil once each day, 5 days/week, for 78 weeks. During the final 26 weeks of treatment, doses were administered to rats in a cyclic pattern of 1 week without treatment followed by 4 weeks with treatment. Body weights and food consumption were obtained weekly for the first 10 weeks and monthly thereafter. Mice and rats were permitted to survive an additional 12 and 32 weeks after treatment, respectively, until sacrifice.

Each animal was submitted to extensive gross and microscopic examinations. Specified organs, plus any other tissue containing visible lesions, were fixed in 10% buffered formalin, embedded in paraplast, and sectioned for slides. Hematoxylin and eosin staining (H and E) was used routinely, but other stains were employed when needed. Diagnoses of observed tumors and other lesions were coded according to a modified Systematized Nomenclature of Pathology (SNOP) originally developed by the College of American Pathologists in 1965.

Tetrachloroethylene was found to be carcinogenic in mice in this study. Results summarized in Table 9-1 indicate that tetrachloroethylene induced highly statistically significant ($P < 0.001$) increases in the incidence of hepatocellular carcinomas in both sexes of mice in both treatment groups as compared to untreated controls or vehicle-controls. The microscopic appearance of carcinomas was variable, with some tumors composed of well-differentiated hepatocytes arranged in rather uniform hepatic cords, and other lesions consisting of anaplastic cells, often with inclusion bodies with vacuolated, pale cytoplasm. Mitotic figures were often present. In male mice, the first hepatocellular carcinomas were detected at 27 weeks in the low-dose group, 40 weeks in the high-dose group,

TABLE 9-1. INCIDENCE OF HEPATOCELLULAR CARCINOMAS IN B6C3F1 MICE FED TETRACHLOROETHYLENE
(National Cancer Institute 1977a)

Dose (mg/kg/day)[a]	Hepatocellular carcinomas	P values[b]
Male		
untreated	2/17 (12%)	
vehicle-control	2/20 (10%)	
536	32/49 (65%)	$P < 0.001$
1072	27/48 (56%)	$P < 0.001$
Female		
untreated	2/20 (10%)	
vehicle-control	0/20 (0%)	
386	19/48 (40%)	$P < 0.001$
772	19/48 (40%)	$P < 0.001$

[a] Time-weighted average doses.

[b] Probability level (P-values) for the Fisher Exact Test comparison of dose groups with vehicle-control group.

and 90 and 91 weeks in vehicle-control and untreated control groups. In female mice, the first hepatocellular carcinomas were observed at week 41 in the low-dose group, week 50 in the high-dose group, and week 91 in the untreated control group. Metastases of hepatocellular carcinomas occurred in the kidneys of one untreated control male and in the lung of three low-dose males, one low-dose female, and one high-dose female.

Toxic nephropathy in mice was apparent in 40/49 low-dose males, 45/48 high-dose males, 46/48 low-dose females, and 48/48 high-dose females. Control animals did not exhibit this lesion. Chronic murine pneumonia was also a frequently observed finding. A low incidence of bloating or abdominal distension was noted in treated animals during the second year of the study. Body weight gain was comparable between groups (Figure 9-1). Median survival times were greater than 90 weeks in control males, 78 weeks in low-dose males, and 43 weeks in high-dose males (Figure 9-2). Median survival times for females were greater than 90 weeks in control females, 62 weeks in low-dose females, and 50 weeks in high-dose females (Figure 9-2).

In rats, toxic nephropathy, not found in control animals, was detected in 43/49 low-dose males, 47/50 high-dose males, 29/50 low-dose females, and 39/50 high-dose females. Figure 9-3 indicates that treated rats gained less weight than controls, though the difference was slight, with maximum reduction being 13% during the first year and 19% during the second year. Clinical signs apparent in treated animals included a hunched appearance and urine stains on the lower abdomen. Respiratory abnormalities, characterized by dyspnea, wheezing, and/or reddish nasal discharge, were noted with increased incidence in all groups during aging of the animals, and chronic murine pneumonia was diagnosed in $\geq$ 62% of the animals in each group. As indicated in Figure 9-4, median survival times were greater than 88 weeks in the control groups, 68 weeks in low-dose females, 66 weeks in high-dose females, 67 weeks in low-dose males, and 44 weeks in high-dose males. The survival was not adequate to support any conclusions about the carcinogenicity of tetrachloroethylene in rats.

In an attempt to characterize impurities present in the tetrachloroethylene product used in this study, documented chemical analyses of the test samples performed at the carcinogenicity testing laboratory of the NCI bioassay program were examined by the analytical department of the Diamond Shamrock Corporation (interoffice memorandum from E. A. Rowe to G. K. Hatfield, Diamond Shamrock Corporation, October 8, 1979, obtained with the documented chemical analyses from G. K. Hatfield, January 28, 1981). As indicated in the interoffice memorandum, tetrachloroethylene samples used in the National Cancer Institute bioassay (NCI 1977a) were not available for analysis at Diamond Shamrock; however, the analytical method, with the same type of instrument and column used at the carcinogenicity testing laboratory, was reproduced. Evaluation of the analytical method led to the conclusions presented in the previously mentioned memorandum that the method could not distinguish epichlorohydrin from trichloroethylene, and that the tetrachloroethylene product used in the NCI (1977a)

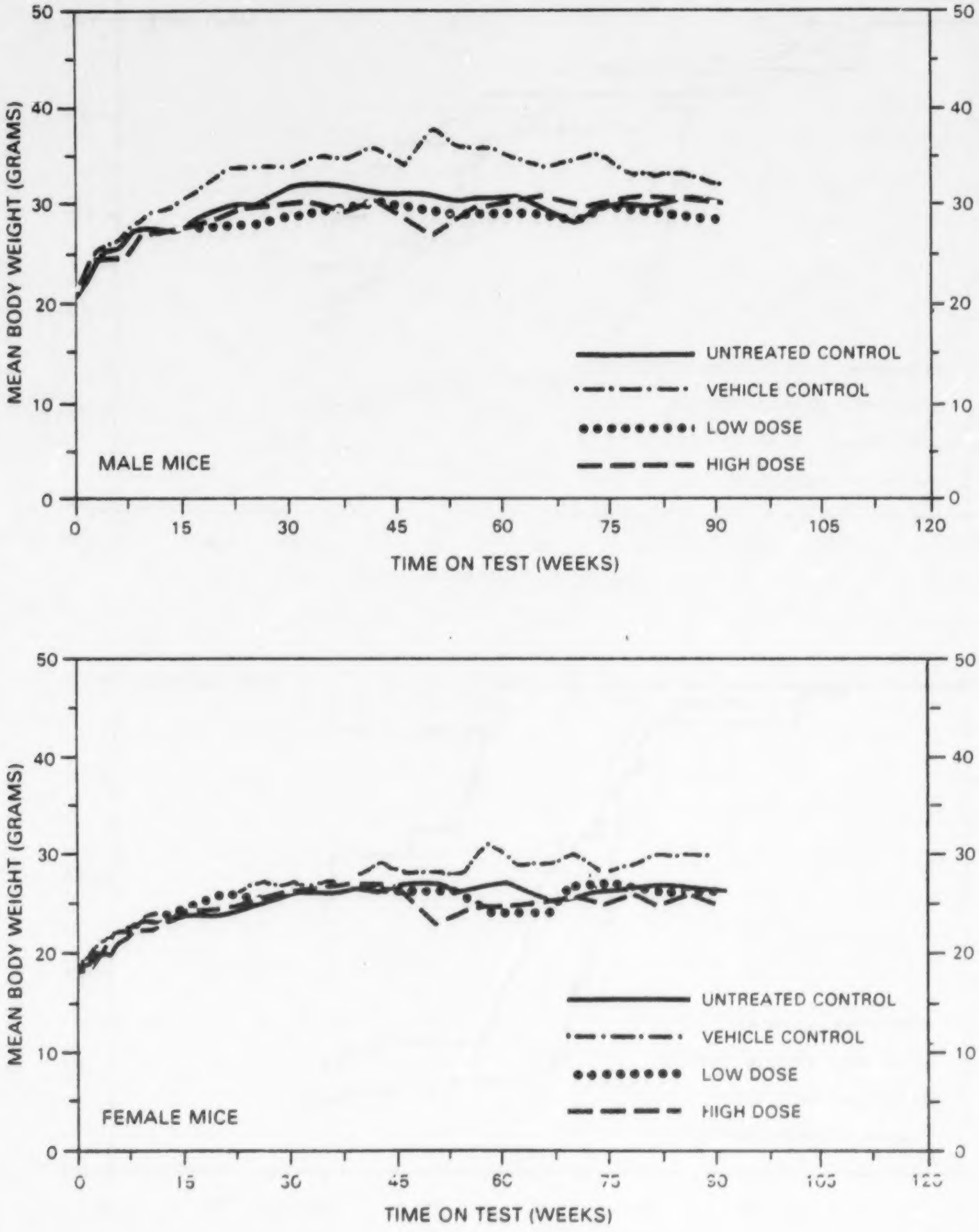

Figure 9-1. Growth curves for male and female mice in the tetrachloroethylene chronic study. (National Cancer Institute 1977a).

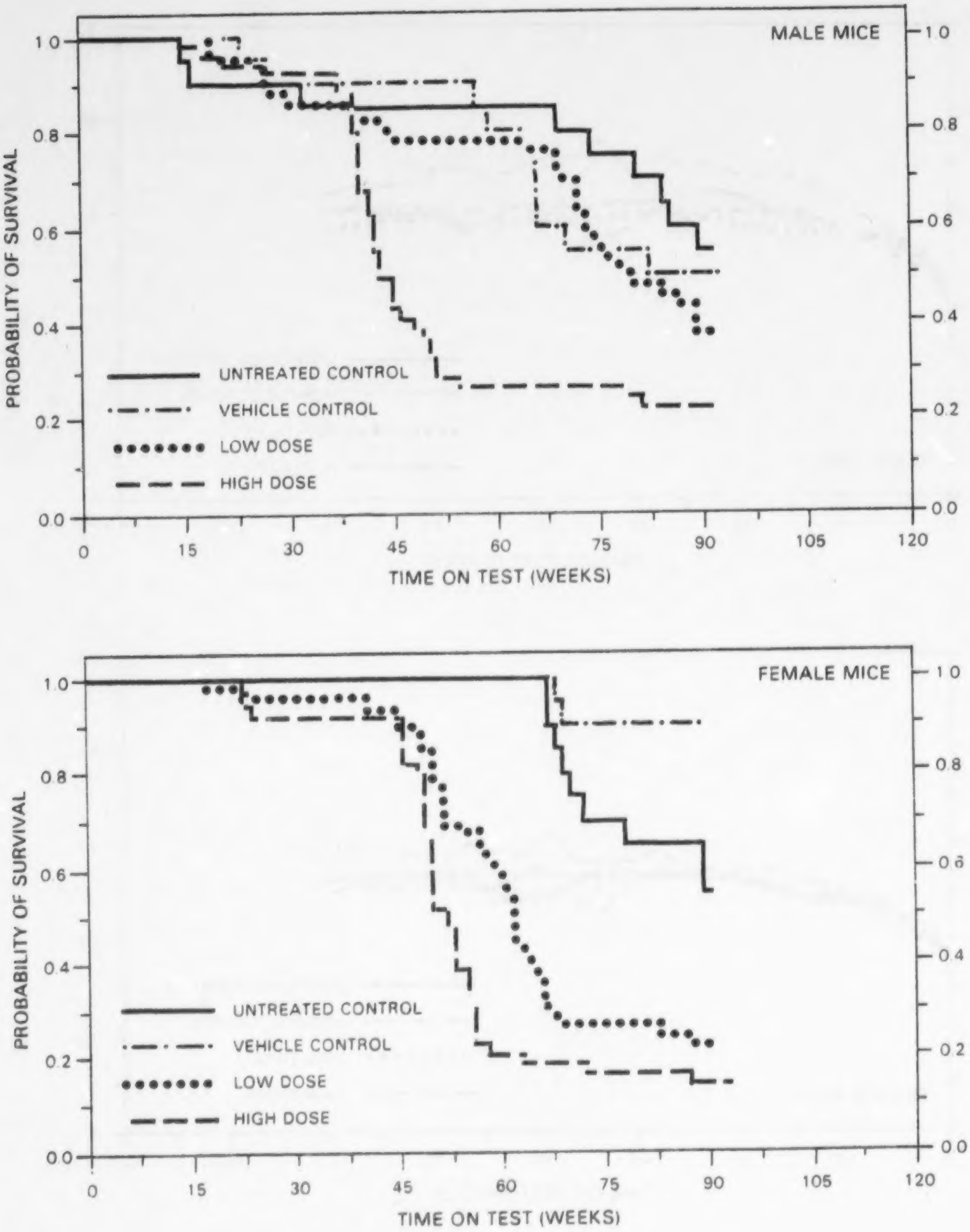

Figure 9-2. Survival comparisons of male and female mice in the tetrachloroethylene chronic study. (National Cancer Institute 1977a).

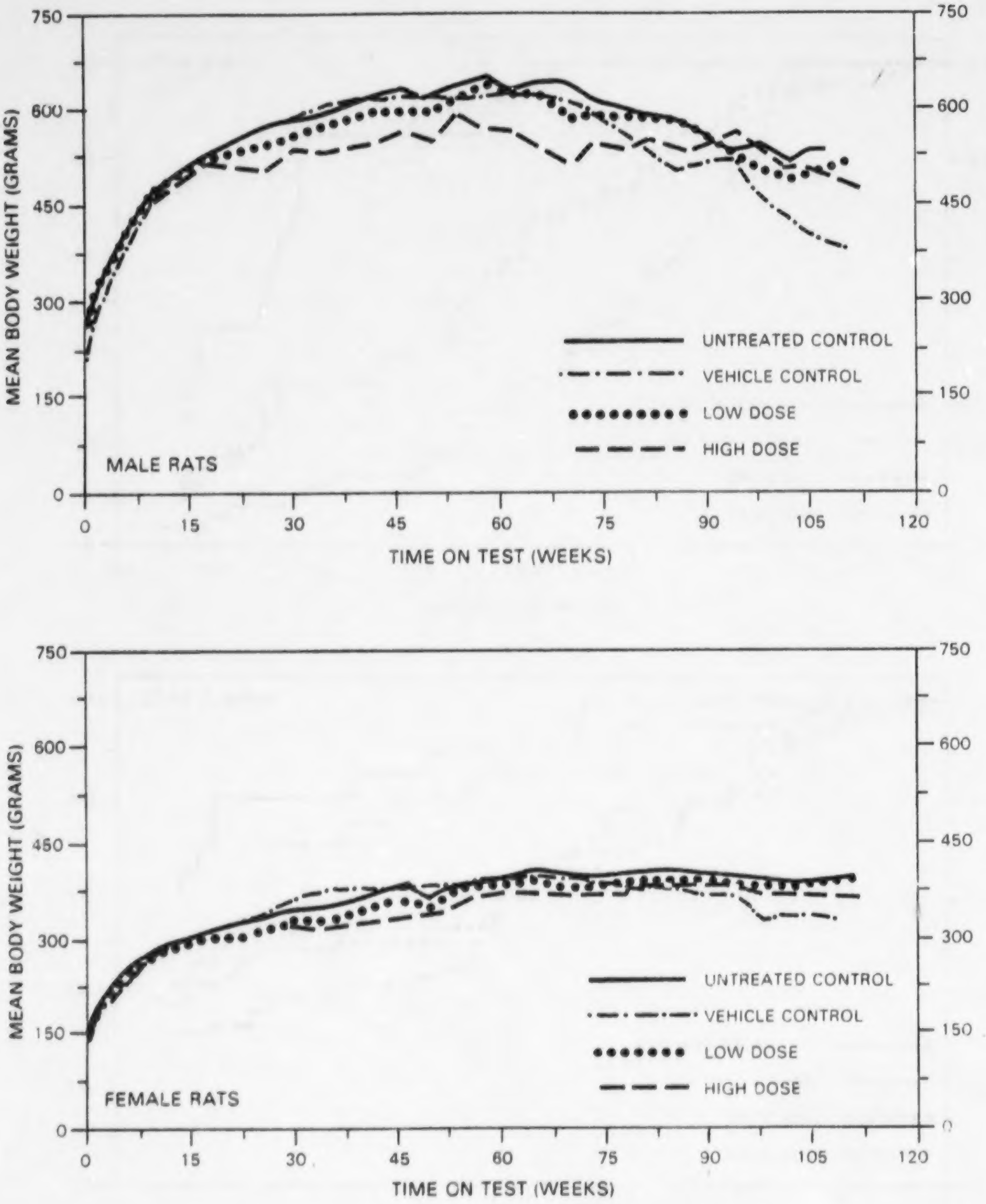

Figure 9-3. Growth curves for male and female rats in the tetrachloroethylene chronic study. (National Cancer Institute 1977a).

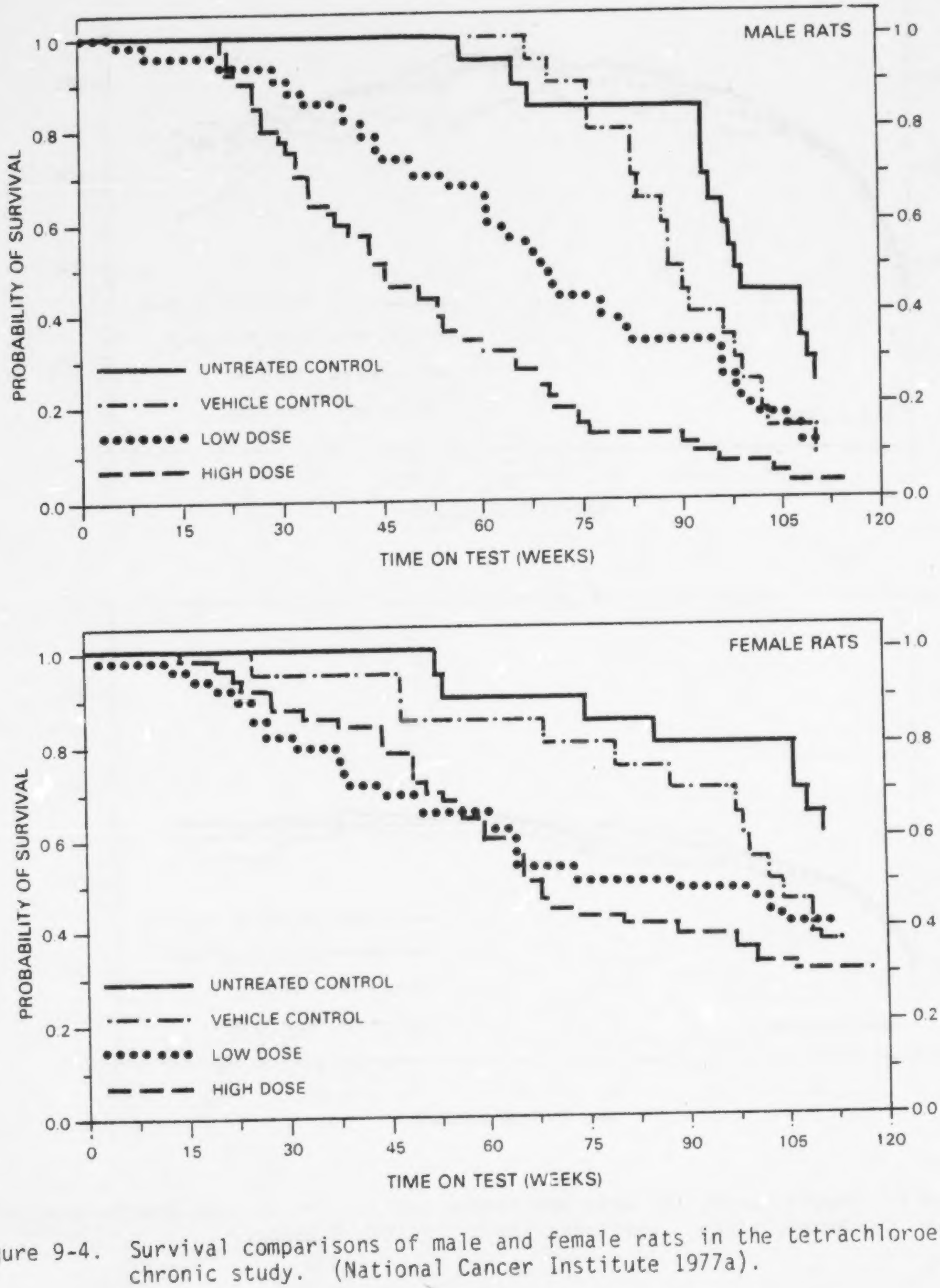

Figure 9-4. Survival comparisons of male and female rats in the tetrachloroethylene chronic study. (National Cancer Institute 1977a).

bioassay could have contained one or both of these compounds as impurities. The documented chemical analyses show contaminant levels of 0.055%, 0.041%, and 0.010% in tetrachloroethylene samples analyzed at the beginning of the bioassay, at 1 year into the bioassay, and at 2 years into the bioassay, respectively. The conclusion stated in the memorandum is that the contaminant was probably epichlorohydrin, since: 1) epichlorohydrin was a commonly used stabilizer for tetrachloroethylene at that time; 2) a reported analysis by a competitor of Diamond Shamrock showed a maximum of 0.015% trichloroethylene in any tetrachloroethylene product manufactured in the United States, and 3) the decreased amount of impurity found in the tetrachloroethylene samples as the bioassay progressed suggests some decomposition in that, according to the experience of Diamond Shamrock, epichlorohydrin but not trichloroethylene levels would decrease during storage. Nonetheless, although the evidence provided by Diamond Shamrock indicates that epichlorohydrin was present in the tetrachloroethylene product used in the NCI (1977a) bioassay, the quantity of epichlorohydrin in the test material used in this study remains uncertain. Furthermore, the different levels of unknown material shown in the documented chemical analysis may be due to the use of the indicated different lots, possibly containing unequal amounts of impurities.

An estimate of the likelihood that the epichlorohydrin impurity in the tetrachloroethylene material used in the NCI experiment could have been large enough to account for the positive results can be obtained by considering the results of Laskin et al. (1980), who exposed rats to epichlorohydrin via inhalation. They found that 1/100 rats exposed to 30 ppm (0.115 mg/l air, equivalent to 13.2 mg/kg/day) of epichlorohydrin for 6 hours/day, 5 days/week, for 730 days developed squamous cell nasal carcinomas, compared with 0/50 in control animals.

The epichlorohydrin impurity in the NCI tetrachloroethylene high-dose male mice experiment was approximately 1,032 mg/kg/day x 0.041% = 0.42 mg/kg/day, from the discussion above. This is only about $0.42/13.2 \approx 0.03$ times the dose that gave an incidence of only 1/100 in the Laskin et al. rat experiment. Therefore, it is unlikely that epichlorohydrin impurities at the level estimated to be present in the NCI experiment could have contributed appreciably to the positive response.

In a second carcinogenicity bioassay sponsored by the National Toxicology Program (NTP 1983, draft), tetrachloroethylene was given orally to B6C3F1 mice and to four strains of rats (Sherman, Fischer 344, Long-Evans, and Wistar). The tetrachloroethylene sample used in this ongoing carcinogenicity bioassay did not contain detectable amounts of epoxide contaminants. In the study with female B6C3F1 mice (NTP 1983, draft), groups of 100 females received 25, 50, 100, or 200 mg of more than 99% pure tetrachloroethylene per kg body weight in corn oil by gavage for 103 weeks, 5 days/week. Vehicle-control and untreated control groups of 100 mice each were used. Survival was not affected significantly. Doses of 50 mg/kg or more produced a dose-related cytomegaly of the kidneys. Other signs of liver toxicity appeared during the study as increases of sorbitol dehydrogenase activity, and increases in relative liver weight and lipid levels were associated with increasing dose levels. Doses of 50 mg/kg or more produced time- and dose-related increases in the incidence of hepatocellular adenomas and carcinomas bearing no causal relationship to the observed renal damage. The first adenoma appeared at week 46; the first carcinoma at week 58. The NTP intends to conduct an audit of the raw data of this study before the final technical report is prepared. The findings of the audit will determine the validity of the study. If the audit reveals no major problems, the NTP expects to present the report to a peer review group no sooner then early 1984 (letter from Dr. Schetz, NTP, to Dr. Haberman, CAG, September 29, 1983).

9.1.2 Dow Chemical Company Inhalation Study (Rampy et al. 1978)

Two groups of weanling Sprague-Dawley (Spartan substrain) rats, each composed of 96 males and 96 females, were exposed to 600 ppm (4.07 mg/l air) or 300 ppm (2.03 mg/l air) of tetrachloroethylene 6 hours/day, 5 days/week, for 52 weeks. An untreated group of 192 males and 192 females served as controls. Controls were not put in inhalation chambers, but were in the treatment room during exposure. At the end of the treatment period of 52 weeks, animals were allowed to survive until sacrifice at 31 months. The composition of the test material (Lot A12282D) by gas chromatographic analysis was as follows: trichloroethylene, 3 ppm (liquid volume %); hexachloroethane, < 12 ppm; carbon tetrachloride, 2 ppm; 4-methyl morpholine, 44 ppm; nonvolatile residue, 2 ppm; tetrachloroethylene, balance. Exposure was done in 3.7 m^3 inhalation chambers with a dynamic airflow system. Analyses of tetrachloroethylene levels in the inhalation chambers during the treatment period revealed analytical concentrations (mean ± standard deviation) of 310 ± 32 ppm (244 analyses) and 592 ± 62 ppm

(1,245 analyses). Analytical concentrations by infrared analysis within ± 10% of nominal levels were achieved on 89.3% (low-dose) and 97.1% (high-dose) of the exposure days. Animals were evaluated for clinical toxic signs, body weight changes, urinalysis at 24 months, and hematology at 12 and 24 months. Survivors and decedents were given gross and histopathologic examinations. Bone marrow samples were taken from three males and three females in each group sacrificed at 1 year for cytogenetic evaluation.

Clinical signs of toxicity were not observed with the nominal concentrations of tetrachloroethylene used in this study. Mean body weight gains were similar among groups. Hematology and urine analyses showed no treatment-related effects of tetrachloroethylene. The mortality patterns exhibited in the study are described in Table 9-2. Mortality in high-dose males was slightly greater than that of controls during months 5 to 24; the earlier onset of chronic renal disease in this treatment group was considered to be a contributing factor in increased mortality.

No carcinogenic effects of tetrachloroethylene were observed from pathologic examination of the animals. Statistical analysis of the data showed numerous non-neoplastic abnormalities that occurred spontaneously and were within the normal variation encountered in lifetime studies with this strain of rat. With respect to tumor findings, statistical analysis of the data did not reveal a definite increased tumor incidence in animals exposed to tetrachloroethylene. Tumors or tumor-like changes in the kidney were found in 1/189 control, 2/94 low-dose, and 4/94 high-dose males during gross necropsy; however, light microscopic examination of kidney lesions did not show a statistically significant tumor incidence compared to controls. Although many tumor types were found in treated and control animals, there was no statistically significant ($P > 0.05$) increase in tumor incidence at any anatomical site.

The results of this study do not indicate a definite carcinogenic effect of tetrachloroethylene in Sprague-Dawley rats; i.e., the tumor incidence between control and treated rats was similar. However, this study has the following drawbacks: 1) the period of exposure was only 12 months rather than the lifetime of the animals, which would have been a more appropriate duration for carcinogenicity studies; and 2) the dose levels in this study do not appear to have been high enough to provide maximum sensitivity.

TABLE 9-2. CUMULATIVE SURVIVAL OF SPRAGUE-DAWLEY RATS EXPOSED TO TETRACHLOROETHYLENE FOR 12 MONTHS
(adapted from Rampy et al. 1978)

Month of Study	0 ppm		300 ppm		600 ppm	
	Male	Female	Male	Female	Male	Female
Initial	189	189	94	91	94	94
6	187	188	94	91	88[a]	94
12	183	185	91	91	84[a]	91
18	155	151	74	77	55[a]	86[a]
24	44	70	26	37	13[a]	49[a]
31	1	12	1	6	1	5

[a] $P < 0.005$ by the Fisher Exact Test.

9.1.3 Intraperitoneal Administration Study (Theiss et al. 1977)

Theiss et al. (1977) tested tetrachloroethylene for carcinogenicity in the strain A mouse pulmonary tumor induction system. The test sample, a product of the Aldrich Chemical Company, was reagent grade with a purity exceeding 95 to 99%. Strain A/St male mice, 6 to 8 weeks old, were used in this assay. The maximum tolerated dosage, defined as the dosage which five mice tolerated after six intraperitoneal injections over a 2-week period followed by a 4-week observation period, was determined and used in the bioassay. In the main test, 20 mice per treatment group received three intraperitoneal injections of 80, 200, or 400 mg/kg of tetrachloroethylene weekly until total dosages of 1120, 4800, and 9600 mg/kg, respectively, were achieved. Survivors were sacrificed at 24 weeks after the first injection, and the number of surface adenomas was counted. Results were compared with findings in vehicle (tricaprylin) and untreated controls by the Student t test. Tetrachloroethylene did not statistically increase ($P > 0.05$) the incidence of pulmonary tumors in this study (Table 9-3). This strain was sensitive to the positive control chemical urethan, as shown in Table 9-3.

TABLE 9-3. PULMONARY TUMOR RESPONSE TO TETRACHLOROETHYLENE (adapted from Theiss et al. 1977)

Compound	Dosage (mg/kg)	No. survivors/ No. animals	No. lung tumors/mouse
Tricaprylin	---	46/50	0.39 ± 0.06[a]
Tetrachloroethylene	80	15/20	0.27 ± 0.07
	200	17/20	0.41 ± 0.10
	400	18/20	0.50 ± 0.12
Urethan	1,000 mg/kg (1 injection)	20/20	19.6 ± 2.4

[a] Mean ± S.E.

A negative result in this assay is not considered conclusive, since several chemicals known to be carcinogenic in chronic rodent bioassays induce no response in this assay.

The strain A mouse pulmonary tumor assay is relatively insensitive to mouse carcinogens for which the effect is confined to the liver (Theiss et al. 1977). For example, chloroform, 2-chloroethyl ether, and hexachlorocyclohexane induce tumors of the liver (not other sites) in mice (NCI 1976, 1977c; Innes et al. 1969) but were not carcinogenic in the assay by Theiss et al. (1977). The reasons for the negative lung response are not understood, but it may be due to a smaller concentration of activating enzymes in the lung than in the liver.

9.1.4 Skin Painting Study (Van Duuren et al. 1979)

A carcinogenicity study of purified tetrachloroethylene in ICR/Ha Swiss mice was described by Van Duuren et al. (1979). Maximum tolerated dosages were determined in range-finding studies 6 to 8 weeks in duration, and were selected as dosages that did not affect body weight gain or produce clinical signs of toxicity. This study included the following experiments: 1) 30 females were treated topically on the dorsal skin with a single application of 163 mg tetrachloroethylene followed 14 days later by the applications of 5.0 ug phorbol myristate acetate (PMA) to the skin three times weekly until termination of the study at 428 to 576 days; median survival time was 428 to 576 days. 2) 30 females were given thrice weekly topical applications of 54 mg tetrachloroethylene for the duration of the test (440 to 594 days) with a median survival time of 317 to 589 days. A vehicle (acetone) control group of 30 mice and an untreated control group of 100 mice were included in these experiments.

In the initiation-promotion experiment, 210 mice treated with PMA alone were also on test. The mice were 6 to 8 weeks old at the beginning of the study, and were housed six to a cage. Test sites on the skin were shaved as necessary and were not covered; however, it was the authors' impression that tetrachloroethylene was immediately absorbed and that evaporation from test sites was minimal (personal communication, B. L. Van Duuren, New York University). The animals were weighed monthly, and each animal was examined by necropsy. Tumors and lesions as well as skin, liver, stomach, and kidneys were examined histologically.

Tetrachloroethylene did not show initiating activity in the initiation-promotion experiment; the number of mice with skin papillomas (squamous cell carcinomas) was: 4 (0) initiated with tetrachloroethylene, 15 (3) treated with PMA alone, and 0 (0) in the control groups. The study involving repeated application to the skin produced lung and stomach tumors in 16 and 0 tetrachloroethylene-treated mice, respectively; 11 and 2 vehicle-treated controls, respectively; and 30 and 5 untreated controls, respectively.

The negative results for tetrachloroethylene in mouse skin as an initiator and as a complete carcinogen can be reconciled with the positive mouse liver response in the NCI study if it is hypothesized that the skin does not have the necessary enzymes to convert tetrachloroethylene to an active metabolite, whereas the liver does have this capability.

The lack of sensitivity of skin application tests, as compared with tests using other routes of exposure, is apparent from the results of Van Duuren et al. (1979) with 1-chloroprene, *cis*-1,3-dichloropropene, and 2-chloroproponal. They found that none of the three compounds induced a response as initiators in initiation-promotion experiments or with repeated topical application on the skin. However, they did observe a statistically significant increase in the incidence of forestomach tumors in female Ha:ICR Swiss mice dosed by gavage with 1-chloroprene ($P < 0.0005$) and 2-chloroproponal ($P < 0.05$) and in the incidence of local sarcomas in female Ha:ICR Swiss mice treated with *cis*-1,3-dichloropropene ($P < 0.0005$) by subcutaneous injection.

9.2 EPIDEMIOLOGIC STUDIES

There are six epidemiologic studies that relate to tetrachloroethylene exposure. Only one of these studies, however, has actually identified workers exposed to tetrachloroethylene. Because tetrachloroethylene has been used in the dry-cleaning industry, the present discussion also includes three proportionate mortality studies of decedents who had worked in the dry-cleaning industry, as well as two case-control studies in which the cases and controls were asked about their employment histories, including employment in the dry-cleaning industry.

9.2.1 Kaplan (1980)

Kaplan (1980) did a retrospective cohort mortality study of dry-cleaning workers exposed to tetrachloroethylene for at least one year prior to 1960. The study was performed under contract to the Biometry Section of the National Institute for Occupational Safety and Health (NIOSH) Industry-Wide Studies Branch.

In a preface to the discussion of the study, Kaplan reported that levels of tetrachloroethylene exposure were "much higher" for cleaners (machine operators) than for other employees of dry-cleaning establishments. A geometric mean time-weighted average for tetrachloroethylene was 22 ppm for the machine operators. For all other jobs, the highest corresponding value was reported to be 3.3 ppm. These data were provided through a NIOSH industrial hygiene survey of dry-cleaning facilities.

The study cohort, selected from records maintained by several labor unions, consisted of 1,597 individuals employed more than 1 year prior to 1960 in dry-cleaning establishments. The primary solvent was tetrachloroethylene. Efforts were made by the author to exclude all persons with previous occupational exposure to carbon tetrachloride or trichloroethylene. By September 30, 1977, the end of the study period, 1,058 individuals were found to be alive, 285 were deceased, and 254 were of unknown vital status. The extent of follow-up varied by sex; 8% of the males and 20.4% of the females remained lost to follow-up. Race was known only for deceased workers, and was obtained from death certificate data. Because of the lack of information regarding race, observed deaths by cause were compared to expected deaths by means of a standardized mortality ratio (SMR) for whites, an SMR for blacks, and a composite point estimate SMR for both. Based on the assumption that every member of the cohort was white, expected deaths for whites were derived by multiplying the person-years accumulated for the entire cohort by the white death rates within 5-year age groups (separately for males and females and then with the two combined). Expected deaths for blacks were similarly generated by assuming that all cohort members were black. Composite expected deaths were calculated by weighting the total accumulated person-years for the cohort in each 5-year age group by the proportion of person-years attributable to the deceased blacks and the proportion attributable to deceased whites, and then multiplying each total separately by the corresponding death rates for whites and blacks, and finally adding across age groups to get the "composite" expected deaths.

Because death certificates could not be located for all of the deceased, it was assumed that those deaths for which no death certificates could be found had the same distribution by cause as those for which death certificates were available. Thus the SMRs for each cause of death were corrected to reflect the missing death certificates. Using the SMR for deaths from malignant neoplasms of the colon in whites as an example, this correction was made in the following manner:

$$\frac{(11/247 \times 38) + 11}{11} \times \frac{11}{6.98} \times 100 = 182$$

where: 247 is the number of deaths in the cohort with death certificates;

38 is the number of deaths in the cohort without death certificates;

11 is the observed number of colon cancer deaths identified by death certificates;

6.98 is the expected number of white colon cancer deaths;

100 is a constant used in calculating SMRs (by convention, SMRs are expressed as a factor of 100); and

182 is the corrected white colon cancer SMR.

No significance tests of any of the SMRs were done by the author. However, the author called attention to the elevated SMR from malignant neoplasms of the colon as possibly related to occupational exposure (6.98 white expected deaths, 6.77 black expected deaths, and composite SMR = 182). Using an observed number of colon cancer cases corrected for the loss of death certificates, the Carcinogen Assessment Group (CAG) found that the SMR for either whites or blacks would be statistically signficant ($P < 0.05$).

The author points out that because the expected numbers of deaths were calculated using U.S. rates, which include a higher socioeconomic class than the dry-cleaners in this study, and because higher socioeconomic class is associated with a risk of colon cancer, the risk of colon cancer from exposure to tetrachloroethylene found in this study is probably underestimated. Furthermore, the expected number of colon cancer cases in this study was calculated using mortality rates for neoplasms of the intestine, except rectum. Although most of the deaths expected using mortality rates for neoplasms of the intestine would be deaths from malignant neoplasms of the colon, some deaths would be from neoplasms of the small intestine. Since all of the observed deaths were from malignant neoplasms of the colon, the comparison of the observed to expected colon cancer deaths in this study would also tend to underestimate the colon cancer risk from exposure to tetrachloroethylene.

It should also be noted that although it could be argued that the number of observed colon cancer deaths in each of the four union locals in this study was small, an elevated colon cancer SMR did exist in each of the four locals. Finally, it should be noted that the colon cancer SMR appeared to demonstrate a positive correlation with the length of the follow-up period. This last finding must be viewed with a great deal of caution, however, because of the author's difficulty in defining length of exposure and hence length of follow-up.

In addition to colon cancer, the SMRs for cancer of various other sites were also elevated. These included rectum, pancreas, respiratory system, urinary organs, and "other and unspecified sites (major)." None of these were significant at the $P < 0.05$ level when tested using an observed number that was corrected for lost death certificates; however, the SMRs for cancer of three of these sites [respiratory system, urinary organs, and "other and unspecified sites (major)"] could be considered borderline significant ($0.10 < P < 0.05$).

Perhaps the major weakness of this study with regard to evaluating tetrachloroethylene as a carcinogen is that the history of solvent exposure prior to 1960 was unknown for nearly half of the union member shops. Because the majority of dry-cleaning establishments in the United States used petroleum distillates as the primary cleaning agent prior to 1960, it is quite likely that most of the shops in this study used petroleum distillates as the cleaning solvent prior to changing to tetrachloroethylene.

Other important confounding variables were also not controlled. For example, smoking is a major confounding variable to be considered when evaluating a potential risk for respiratory or bladder cancer, both of which were found in excess in this study. Socioeconomic status, as has been discussed, is a confounding variable for colon cancer.

Another weakness of this study is that 16 percent of the study cohort was lost to follow-up. Currently, NIOSH is attempting to improve the percentage of follow-up as well as to add to the length of follow-up. In addition, NIOSH has identified other individuals who were exposed to tetrachloroethylene for at least one year prior to 1960, so that the size of the cohort has also been increased.

In summary, this study appears suggestive that dry-cleaning workers exposed to tetrachloroethylene are at an elevated risk of colon cancer mortality. Potential exposure to petroleum distillates for approximately half of the cohort, however, limits any conclusions with regard to the carcinogenicity of tetrachloroethylene in humans.

9.2.2 Blair et al. (1979)

Blair et al. (1979) reported, as the preliminary results of a cohort study of 10,000 laundry and dry-cleaning workers, a proportionate mortality analysis of 330 of the workers who had died during the period 1957-1977. Deaths were identified from the mortality records of two union locals in St. Louis, Missouri. The distribution by cause of death among the 330 was compared to that expected based on the proportionate mortality experience of the United States. Only 279 of the 330 had worked exclusively in dry-cleaning establishments; however, the authors did not report the proportionate mortality analyses of these 279. Furthermore, the dry-cleaning agent used by the dry-cleaners in this study is unknown. Among the 330 deaths, deaths from cancer of the lung, cervix, and skin contributed to the finding of a significant ($P < 0.05$) excess proportion of deaths from cancer at all sites. For lung cancer, there were 17 deaths observed versus 10 expected ($P < 0.05$); for cervical cancer, 10 observed deaths versus 4.8 expected ($P < 0.05$); and for skin cancer, 3 observed deaths versus 0.7 expected ($P < 0.05$). On the other hand, a significant deficit of deaths occurred in the cause category identified as "all circulating diseases," with 100 observed versus 125.9 expected ($P < 0.005$)--a finding which could account for the excess proportion of cancers observed.

Only limited conclusions can be drawn from this study as to the potential carcinogenicity of tetrachloroethylene. This is true for several reasons. First, the study did not report the distribution of deaths for dry-cleaners alone. Second, the dry-cleaning agent these workers used is not known. Lastly, certain possibly confounding variables were not considered in the analysis of the results. These variables include smoking (with regard to the lung cancer excess), socio-economic status (with regard to the cervical cancer excess), and sunlight exposure (with regard to the skin cancer excess).

9.2.3 Katz and Jowett (1981)

Katz and Jowett (1981) analyzed the death certificate records of 671 white female laundry and dry-cleaning workers who had died during the period 1963-1977. The records of dry-cleaning workers were not studied separately from those of laundry workers, since both groups of workers shared the same occupational code. Furthermore, it is not known whether those decedents who were dry-cleaners used tetrachloroethylene as a dry-cleaning agent. During the 1940s, petroleum derivatives were the predominant dry-cleaning agents used in the United States. A shift to the use of tetrachloroethylene began in the late 1940s and gained momentum in the 1950s and 1960s. By 1977, approximately 75% of the dry-cleaning plants in the United States were using tetrachloroethylene. However, in the period before 1960, petroleum distillates were still the dominant solvents in use (Kaplan 1980).

In this study, cause-specific proportionate mortality for the 671 deceased laundry and dry-cleaning workers was compared to that for the deaths of all other working females in Wisconsin during the same period, and to deaths of females in "lower-wage occupations" in Wisconsin during the same period. Significantly elevated proportionate mortality ratios (PMRs) were found for deaths from cancer of the genitals (unspecified) ($P < 0.01$) and for deaths from cancer of the kidney ($P < 0.05$) when deaths among women of all occupations and deaths among women of "lower-wage occupations" were used as the comparison groups. In summary, this study, although suggesting an association of employment in the dry-cleaning industry with excess risks of certain types of cancer, cannot be said to demonstrate conclusively that such an association exists, because of the possible confounding influence of other dry-cleaning agents, and the fact that no distinction was made between laundry and dry-cleaning workers.

9.2.4 Lin and Kessler (1981)

Lin and Kessler (1981) did a case-control study of 109 pancreatic cancer cases diagnosed during the period 1972-1975 from 115 hospitals in five metropolitan areas. The control group was composed of subjects who were free from cancer but who were similar to the study group in age (± 3 years), sex, race, and marital status, and who were selected at random from among contemporaneous admissions to the same hospital. Cases and controls were asked about demographic characteristics, residential history, toxic exposures, animal contacts, smoking habits, diet, medical history, medications, and family history. Males were asked about sexual practices and urogenital conditions. Females were questioned on these topics and also on their marital, obstetric, and gynecologic histories. Among other statistically significant associations, an association was found between pancreatic cancer and employment either as a dry-cleaner or in a job involving exposure to gasoline. It is not known, however, how many individuals with pancreatic cancer were employed as dry-cleaners and how many were employed in occupations involving exposure to gasoline. Furthermore, the dry-cleaners may have used a variety of dry-cleaning agents other than tetrachloroethylene. Thus this study, although suggestive of an association between employment as a dry-cleaner and an excess risk of pancreatic cancer, cannot be said to demonstrate an association between pancreatic cancer and tetrachloroethylene exposure.

9.2.5 Asal (personal communication 1983)

In two epidemiologic studies conducted by Dr. Nabih Asal of the University of Oklahoma, an excess of cancer among dry-cleaners was found (personal communication 1983). These studies are as yet unpublished. One of the studies was a kidney cancer case-control study in which Asal found an association between kidney cancer and the dry-cleaning occupation. The second study was a proportionate mortality study of dry-cleaning workers in Oklahoma. Asal reported that results from the latter study suggest an increased mortality from kidney and lung cancer among the workers. As in the Blair et al., Katz and Jowett, and Lin and Kessler studies previously discussed, exposure in the studies by Asal was not specific for tetrachloroethylene. Moreover, the conclusions of these studies cannot objectively be evaluated until published descriptions of them are available.

9.3 QUANTITATIVE ESTIMATION

This quantitative section deals with estimation of the unit risk for tetrachloroethylene as a potential carcinogen in air and water, and with the potency of tetrachloroethylene relative to other carcinogens that have been evaluated by the CAG. The unit risk for an air or water pollutant is defined as the lifetime cancer risk to humans from daily exposure to a concentration of 1 ug/m^3 of the pollutant in air by inhalation, or to a concentration of 1 ug/l in water by ingestion.

The unit risk estimate for tetrachloroethylene represents an extrapolation below the dose range of experimental data. There is currently no solid scientific basis for any mathematical extrapolation model that relates exposure to cancer risk at the extremely low concentrations, including the unit concentration given above, that must be dealt with in evaluating environmental hazards. For practical reasons the correspondingly low levels of risk cannot be measured directly either by animal experiments or by epidemiologic study. Low-dose extrapolation must, therefore, be based on current understanding of the mechanisms of carcinogenesis. At the present time the dominant view of the carcinogenic process involves the concept that most cancer-causing agents also cause irreversible damage to DNA. This position is based in part on the fact that a very large proportion of agents that cause cancer are also mutagenic. There is reason to expect that the quantal response that is characteristic of mutagenesis is associated with a linear non-threshold dose-response relationship. Indeed, there is substantial evidence from mutagenicity studies with both ionizing radiation and a wide variety of chemicals that this type of dose-response model is the appropriate one to use. This is particularly true at the lower end of the dose-response curve; at high doses, there can be an upward curvature, probably reflecting the effects of multistage processes on the mutagenic response. The linear non-threshold dose-response relationship is also consistent with the relatively few epidemiologic studies of cancer responses to specific agents that contain enough information to make the evaluation possible (e.g., radiation induced leukemia, breast and thyroid cancer, skin cancer induced by arsenic in drinking water, liver cancer induced by aflatoxins in the diet). Some supporting evidence also exists from animal experiments (e.g., the initiation stage of the two-stage carcinogenesis model in rat liver and mouse skin).

Because its scientific basis, although limited, is the best of any of the current mathematical extrapolation models, the non-threshold model, which is linear at low doses, has been adopted as the primary basis for risk extrapolation to low levels of the dose-response relationship. The risk estimates made with such a model should be regarded as conservative, representing the most plausible upper limit for the risk; i.e., the true risk is not likely to be higher than the estimate, but it could be lower.

For several reasons, the unit risk estimate based on animal bioassays is only an approximate indication of the absolute risk in populations exposed to known carcinogen concentrations. First, there are important species differences in uptake, metabolism, and organ distribution of carcinogens, as well as species differences in target site susceptibility, immunological responses, hormone function, dietary factors, and disease. Second, the concept of equivalent doses for humans compared to animals on a mg/surface area basis is virtually without experimental verification as regards carcinogenic response. Finally, human populations are variable with respect to genetic constitution and diet, living environment, activity patterns, and other cultural factors.

The unit risk estimate can give a rough indication of the relative potency of a given agent as compared with other carcinogens. Such estimates are, of course, more reliable when the comparisons are based on studies in which the test species, strain, sex, and routes of exposure are similar.

The quantitative aspect of carcinogen risk assessment is addressed here because of its possible value in the regulatory decision-making process, e.g., in setting regulatory priorities, evaluating the adequacy of technology-based controls, etc. However, the imprecision of presently available technology for estimating cancer risks to humans at low levels of exposure should be recognized. At best, the linear extrapolation model used here provides a rough but plausible estimate of the upper limit of risk--that is, with this model it is not likely that the true risk would be much more than the estimated risk, but it could be considerably lower. The risk estimates presented in subsequent sections should not be regarded, therefore, as accurate representations of the true cancer risks even when the exposures involved are accurately defined. The estimates presented may, however, be factored into regulatory decisions to the extent that the concept of upper-risk limits is found to be useful.

9.3.1 Procedures for the Determination of Unit Risk

9.3.1.1 Low-Dose Extrapolation Model--The mathematical formulation chosen to describe the linear nonthreshold dose-response relationship at low doses is the linearized multistage model. This model employs enough arbitrary constants to be able to fit almost any monotonically increasing dose-response data, and it incorporates a procedure for estimating the largest possible linear slope (in the 95% confidence limit sense) at low extrapolated doses that is consistent with the data at all dose levels of the experiment.

Let P(d) represent the lifetime risk (probability) of cancer at dose d. The multistage model has the form

$$P(d) = 1 - \exp [-q_0 + q_1 d + q_1 d^2 + \ldots + q_k d^k)]$$

where

$$q_i \geq 0, \ i = 0, 1, 2, \ldots, k$$

Equivalently,

$$P_t(d) = 1 - \exp [q_1 d + q_2 d^2 + \ldots + q_k d^k)]$$

where

$$P_t(d) = \frac{P(d) - P(0)}{1 - P(0)}$$

is the extra risk over background rate at dose d.

The point estimate of the coefficients q_i, $i = 0, 1, 2, \ldots, k$, and consequently, the extra risk function, $P_t(d)$, at any given dose d, is calculated by maximizing the likelihood function of the data.

The point estimate and the 95% upper confidence limit of the extra risk, $P_t(d)$, are calculated by using the computer program, GLOBAL79, developed by Crump and Watson (1979). At low doses, upper 95% confidence limits on the extra risk and lower 95% confidence limits on the dose producing a given risk are determined from a 95% upper confidence limit, q_1^*, on parameter q_1. Whenever $q_1 > 0$, at low doses the extra risk $P_t(d)$ has approximately the form $P_t(d) = q_1^* \times d$. Therefore, $q_1^* \times d$ is a 95% upper confidence limit on the extra risk and R/q_1^* is a 95% lower confidence limit on the dose, producing an extra risk of R. Let L_0 be the maximum value of the log-likelihood function.

The upper-limit q_1^* is calculated by increasing q_1 to a value q_1^* such that when the log-likelihood is remaximized subject to this fixed value q_1^* for the linear coefficient, the resulting maximum value of the log-likelihood L_1 satisfies the equation

$$2\ (L_0 - L_1) = 2.70554$$

where 2.70554 is the cumulative 90% point of the chi-square distribution with one degree of freedom, which corresponds to a 95% upper-limit (one-sided). This approach of computing the upper confidence limit for the extra risk $P_t(d)$ is an improvement on the Crump et al. (1977) model. The upper confidence limit for the extra risk calculated at low doses is alway linear. This is conceptually consistent with the linear nonthreshold concept discussed earlier. The slope, q_1^*, is taken as an upper-bound of the potency of the chemical in inducing cancer at low doses. (In the section calculating the risk estimates, $P_t(d)$ will be abbreviated as P.)

In fitting the dose-response model, the number of terms in the polynomial is chosen equal to (h-1), where h is the number of dose groups in the experiment, including the control group.

Whenever the multistage model does not fit the data sufficiently well, data at the highest dose is deleted and the model is refit to the rest of the data. This is continued until an acceptable fit to the data is obtained. To determine whether or not a fit is acceptable, the chi-square statistic

$$X^2 = \sum_{i=1}^{h} \frac{(X_i - N_iP_i)^2}{N_iP_i\ (1-P_i)}$$

is calculated where N_i is the number of animals in the i^{th} dose group, X_i is the number of animals in the i^{th} dose group with a tumor response, P_i is the probability of a response in the i^{th} dose group estimated by fitting the multistage model to the data, and h is the number of remaining groups. The fit is determined to be unacceptable whenever X^2 is larger than the cumulative 99% point of the chi-square distribution with f degrees of freedom, where f equals the number of dose groups minus the number of non-zero multistage coefficients.

9.3.1.2 Selection of Data--For some chemicals, several studies in different animal species, strains, and sexes, each run at several doses and different routes of exposure, are available. A choice must be made as to which of the data sets from several studies to use in the model. It may also be appropriate to correct for metabolism differences between species and for absorption factors via different routes of administration. The procedures used in evaluating these data are consistent with the approach of making a maximum-likely risk estimate. They are as follows:

1. The tumor incidence data are separated according to organ sites or tumor types. The set of data (i.e., dose and tumor incidence) used in the model is the set where the incidence is statistically significantly higher than the control for at least one test dose level and/or where the tumor incidence rate shows a statistically significant trend with respect to dose level. The data set that gives the highest estimate of the lifetime carcinogenic risk, q_1^*, is selected in most cases. However, efforts are made to exclude data sets that produce spuriously high risk estimates because of a small number of animals. That is, if two sets of data show a similar dose-response relationship, and one has a very small sample size, the set of data having the larger sample size is selected for calculating the carcinogenic potency.

2. If there are two or more data sets of comparable size that are identical with respect to species, strain, sex, and tumor sites, the geometric mean of q_1^*, estimated from each of these data sets, is used for risk assessment. The geometric mean of numbers $A_1, A_2, \ldots, A_m$ is defined as

$$(A_1 \times A_2 \times \ldots \times A_m)^{1/m}.$$

3. If two or more significant tumor sites are observed in the same study, and if the data are available, the number of animals with at least one of the specific tumor sites under consideration is used as incidence data in the model.

9.3.1.3 Calculation of Human Equivalent Dosages--Following the suggestion of Mantel and Schneiderman (1975), it is assumed that mg/surface area/day is an equivalent dose between species. Since, to a close approximation, the surface area is proportional to the two-thirds power of the weight, as would be the case for a perfect sphere, the exposure in mg/day per two-thirds power of the weight is also considered to be equivalent exposure. In an animal experiment, this equivalent dose is computed in the following manner.

Let

L_e = duration of experiment

l_e = duration of exposure

m = average dose per day in mg during administration of the agent (i.e., during l_e), and

W = average weight of the experimental animal

Then, the lifetime exposure is

$$d = \frac{l_e \times m}{L_e \times W^{2/3}}$$

9.3.1.3.1 Oral. Often exposures are not given in units of mg/day, and it becomes necessary to convert the given exposures into mg/day. Similarly, in drinking water studies, exposure is expressed as ppm in the water. For example, in most feeding studies exposure is given in terms of ppm in the diet. In these cases, the exposure in mg/day is

$$m = \text{ppm} \times F \times r$$

where ppm is parts per million of the carcinogenic agent in the diet or water, F is the weight of the food or water consumed per day in kg, and r is the absorption fraction. In the absence of any data to the contrary, r is assumed to be equal to one. For a uniform diet, the weight of the food consumed is proportional to the calories required, which in turn is proportional to the surface area, or two-thirds power of the weight. Water demands are also assumed to be proportional to the surface area, so that

$$m \propto \text{ppm} \times W^{2/3} \times r$$

or

$$\frac{m}{rW^{2/3}} \propto \text{ppm}.$$

As a result, ppm in the diet or water is often assumed to be an equivalent exposure between species. However, this is not justified for the present study, since the ratio of calories to food weight is very different in the diet of man as compared to laboratory animals, primarily due to differences in the moisture content of the foods eaten. For the same reason, the amount of drinking water required by each species also differs. It is therefore necessary to use an empirically-derived factor, $f = F/W$, which is the fraction of an organism's body weight that is consumed per day as food, expressed as follows:

		Fraction of body weight consumed as	
Species	W	f_{food}	f_{water}
Man	70	0.028	0.029
Rats	0.35	0.05	0.078
Mice	0.03	0.13	0.17

Thus, when the exposure is given as a certain dietary or water concentration in ppm, the exposure in mg/$W^{2/3}$ is

$$\frac{m}{rW^{2/3}} = \frac{ppm \times F}{W^{2/3}} = \frac{ppm \times f \times W}{W^{2/3}} = ppm \times f \times W^{1/3}$$

When exposure is given in terms of mg/kg/day = $m/Wr = s$, the conversion is simply

$$\frac{m}{rW^{2/3}} = s \times W^{1/3}.$$

9.3.1.3.2 Inhalation. When exposure is via inhalation, the calculation of dose can be considered for two cases where 1) the carcinogenic agent is either a completely water-soluble gas or an aerosol and is absorbed proportionally to the amount of air breathed in, and 2) where the carcinogen is a poorly water-soluble gas which reaches an equilibrium between the air breathed and the body compartments. After equilibrium is reached, the rate of absorption of these agents is expected to be proportional to the metabolic rate, which in turn is proportional to the rate of oxygen consumption, which in turn is a function of surface area.

9.3.1.3.2.1 Case 1. Agents that are in the form of particulate matter or virtually completely absorbed gases, such as sulfur dioxide, can reasonably be expected to be absorbed proportionally to the breathing rate. In this case the exposure in mg/day may be expressed as

$$m = I \times v \times r$$

where I = inhalation rate per day in m^3, v = mg/m^3 of the agent in air, and r = the absorption fraction.

The inhalation rates, I, for various species can be calculated from the observations of the Federation of American Societies for Experimental Biology (FASEB 1974) that 25 g mice breathe 34.5 liters/day and 113 g rats breathe 105 liters/day. For mice and rats of other weights, W (in kilograms), the surface area proportionality can be used to find breathing rates in m^3/day as follows:

$$\text{For mice, } I = 0.0345\ (W/0.025)^{2/3}\ m^3/\text{day}$$

$$\text{For rats, } I = 0.105\ (W/0.113)^{2/3}\ m^3/\text{day}$$

For humans, the value of 30 m^3/day* is adopted as a standard breathing rate (International Commission on Radiological Protection 1977). The equivalent exposure in $mg/W^{2/3}$ for these agents can be derived from the air intake data in a way analogous to the food intake data. The empirical factors for the air intake per kg per day, $i = I/W$, based upon the previously stated relationships, are tabulated as follows:

Species	W	i = I/W
Man	70	0.29
Rats	0.35	0.64
Mice	0.03	1.3

Therefore, for particulates or completely absorbed gases, the equivalent exposure in $mg/W^{2/3}$ is

$$d = \frac{m}{W^{2/3}} = \frac{Ivr}{W^{2/3}} = \frac{iWvr}{W^{2/3}} = iW^{1/3}vr$$

In the absence of experimental information or a sound theoretical argument to the contrary, the fraction absorbed, r, is assumed to be the same for all species.

9.3.1.3.2.2 Case 2. The dose in mg/day of partially soluble vapors is proportional to the O_2 consumption, which in turn is proportional to $W^{2/3}$ and is also proportional to the solubility of the gas in body fluids, which can be expressed as an absorption coefficient, r, for the gas. Therefore, expressing the O_2 consumption as $O_2 = k\ W^{2/3}$, where k is a constant independent of species, it follows that

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*From "Recommendation of the International Commission on Radiological Protection," page 9. The average breathing rate is 10^7 cm^3 per 8-hour workday and 2×10^7 cm^3 in 24 hours.

$$m = k\ W^{2/3} \times v \times r$$

or

$$d = \frac{m}{W^{2/3}} = kvr$$

As with Case 1, in the absence of experimental information or a sound theoretical argument to the contrary, the absorption fraction, r, is assumed to be the same for all species. Therefore, for these substances a certain concentration in ppm or ug/m^3 in experimental animals is equivalent to the same concentration in humans. This is supported by the observation that the minimum alveolar concentration necessary to produce a given "stage" of anesthesia is similar in man and animals (Dripps et al. 1977). When the animals are exposed via the oral route and human exposure is via inhalation or vice versa, the assumption is made, unless there is pharmacokinetic evidence to the contrary, that absorption is equal by either exposure route.

9.3.1.4 Calculation of the Unit Risk from Animal Studies--The risk associated with d mg/kg$^{2/3}$/day is obtained from GLOBAL79 and, for most cases of interest to risk assessment, can be adequately approximated by $P(d) = 1 - \exp(-q_1^* d)$. A "unit risk" in units X is simply the risk corresponding to an exposure of $X = 1$. This value is estimated simply by finding the number of mg/kg$^{2/3}$/day that corresponds to one unit of X, and substituting this value into the above relationship. Thus, for example, if X is in units of ug/m^3 in the air, then for case 1, $d = 0.29 \times 70^{1/3} \times 10^{-3}$ mg/kg$^{2/3}$/day, and for case 2, $d = 1$, when ug/m^3 is the unit used to compute parameters in animal experiments.

If exposures are given in terms of ppm in air, the following calculation may be used:

$$1 \text{ ppm} = 1.2 \times \frac{\text{molecular weight (gas)}}{\text{molecular weight (air)}} \text{ mg/m}^3$$

Note that an equivalent method of calculating unit risk would be to use mg/kg for the animal exposures, and then to increase the j^{th} polynomial coefficient by an amount

$$(W_h/W_a)^{j/3} \quad j = 1, 2, \ldots, k,$$

and to use mg/kg equivalents for the unit risk values.

9.3.1.4.1 Adjustments for Less Than Lifespan Duration of Experiment. If the duration of experiment L_e is less than the natural lifespan of the test animal L, the slope q_1^*, or more generally the exponent g(d), is increased by multiplying a factor $(L/L_e)^3$. We assume that if the average dose d is continued, the age-specific rate of cancer will continue to increase as a constant function of the background rate. The age-specific rates for humans increase at least by the third power of the age and often by a considerably higher power, as demonstrated by Doll (1971). Thus, it is expected that the cumulative tumor rate would increase by at least the third power of age. Using this fact, it is assumed that the slope q_1^*, or more generally the exponent g(d), would also increase by at least the third power of age. As a result, if the slope q_1^* [or g(d)] is calculated at age L_e, it is expected that if the experiment had been continued for the full lifespan L at the given average exposure, the slope q_1^* [or g(d)] would have been increased by at least $(L/L_e)^3$.

This adjustment is conceptually consistent with the proportional hazard model proposed by Cox (1972) and the time-to-tumor model considered by Daffer et al. (1980), where the probability of cancer by age t and at dose d is given by

$$P(d,t) = 1 - \exp[-f(t) \times g(d)].$$

9.3.1.5 Model for Estimation of Unit Risk Based on Human Data--If human epidemiologic studies and sufficiently valid exposure information are available for the compound, they are always used in some way. If they show a carcinogenic effect, the data are analyzed to give an estimate of the linear dependence of cancer rates on lifetime average dose, which is equivalent to the factor B_H. If they show no carcinogenic effect when positive animal evidence is available, then it is assumed that a risk does exist, but it is smaller than could have been observed in the epidemiologic study, and an upper-limit to the cancer incidence is calculated assuming hypothetically that the true incidence is below the level of detection in the cohort studied, which is determined largely by the cohort size. Whenever possible, human data are used in preference to animal bioassay data.

Very little information exists that can be utilized to extrapolate from high exposure occupational studies to exposures at low environmental levels. However, if a number of simplifying assumptions are made, it is possible to construct a crude dose-response model whose parameters can be estimated using vital statistics, epidemiologic studies, and estimates of worker exposures.

In human studies, the response is measured in terms of the relative risk of the exposed cohort of individuals as compared with the control group. The mathematical model employed for the low-dose extrapolation assumes that for low exposures the lifetime probability of death from cancer, P_0, may be represented by the linear equation

$$P_0 = A + B_H x$$

where A is the lifetime probability in the absence of the agent, and x is the average lifetime exposure to environmental levels in units such as ppm. The factor B_H is the increased probability of cancer associated with each unit increase of x, the agent in air.

If it is assumed that R, the relative risk of cancer for exposed workers as compared to the general population, is independent of length of exposure or age at exposure, and depends only upon average lifetime exposure, it follows that

$$R = \frac{P}{P_0} = \frac{A + B_H (x_1 + x_2)}{A + B_H x_1}$$

or

$$RP_0 = A + B_H (x_1 + x_2)$$

where x_1 = lifetime average daily exposure to the agent for the general population, x_2 = lifetime average daily exposure to the agent in the occupational setting, and P_0 = lifetime probability of dying of cancer with no or negligible exposure.

Substituting $P_0 = A + B_H x_1$ and rearranging gives

$$B_H = P_0 (R - 1)/x_2$$

To use this model, estimates of R and x_2 must be obtained from epidemiologic studies. The value P_0 is derived by means of the life table methodology from the age- and cause-specific death rates for the general population found in U.S. vital statistics tables.

9.3.2 Unit Risk Estimates

9.3.2.1 Data Available for Potency Calculation--The data on hepatocellular carcinomas in B6C3F1 female mice, as reported in the NCI gavage study (1977a), constitute the only information available for use in estimating the carcinogenic potency of tetrachloroethylene. Because of the high mortality and early tumor occurrence in the animals treated with tetrachloroethylene in the above study, the data on times-to-death cited therein have been used in the present report for potency calculations. These data, along with the results of the calculations, are presented in Appendix B. For comparison, the study's incidence of hepatocellular carcinomas (Table 9-4) is also utilized, employing four different extrapolation models.

TABLE 9-4. INCIDENCE RATE OF HEPATOCELLULAR CARCINOMAS IN FEMALE B6C3F1 MICE (NCI 1977a)

Experimental dose (mg/kg/day)	Human equivalent dose (mg/kg/day)[a]	Tumor incidence[b]
0	0	0/20
386	18.02	19/48 (40%)
772	36.04	19/45 (42%)

[a] The human equivalent dose is calculated by d x (5/7) x (78/90) x $(0.03/70)^{1/3} = 4.67 \times 10^{-2}$ x d, where d is the experimental dose given to animals 5 days per week for 78 weeks. The lifespan of mice is assumed to be 90 weeks. The factor $(0.03/70)^{1/3}$ is the cubic root of the ratio of body weights between animals and humans. The use of this factor assumes that the doses in mg per body surface are equally effective between mice and humans. For comparison, the potency is also calculated when mg/kg/day is assumed to be the equally effective dosage between mice and humans.

[b] Denominators are the numbers of animals that survived beyond 40 weeks. The time to the first tumor is 41 weeks.

There is no sound human epidemiologic data presently available that can be used to calculate the cancer risk of tetrachloroethylene. However, existing human data can be used for arriving at rough estimates of the magnitude of human cancer risk from exposure to tetrachloroethylene, and for comparison with potency estimates made on the basis of animal data. The colon cancer mortality data presented in the NIOSH report (Kaplan 1980) have been used for this purpose. A detailed discussion of that study, focusing particularly on its investigation of colon cancer, was presented above in the epidemiology section of this chapter.

9.3.2.2 Assumption About Equally Potent Doses--To convert animal doses to human doses, it is assumed that mg/surface area/day is equivalent among species. This assumption is suggested by Mantel and Schneiderman (1975) and is supported empirically in comparing the toxicity of anticancer agents in various animal species and man (Freireich et al. 1966, Rall 1977). Under this assumption, the animal dose d, in mg/kg/day, is multiplied by a factor $(W_a/W_h)^{1/3}$ to obtain the human equivalent dose, where W_a and W_h are, respectively, the animal and human body weights. Another approach to interspecies extrapolation that has been used in risk assessment is direct extrapolation on the basis of body weight (i.e., mg/kg/day). In the present report, the risks calculated on the basis of body weight are also provided. The carcinogenic potency per mg/kg/day calculated on the basis of body surface area is always higher than when calculated on the basis of body weight. However, the fact that the calculated potency expressed in a particular unit, $(\text{mg/kg/day})^{-1}$, is higher on the basis of surface area does not necessarily imply that humans are assumed to be more sensitive than animals. This would be the case if doses in mg/kg/day were in reality equally potent between humans and animals.

9.3.2.3 Choice of Low-Dose Extrapolation Models--In addition to the multistage model currently used by the CAG for low-dose extrapolation, three more models, referred to as the probit, the Weibull, and the one-hit models, are employed for purposes of comparison (Appendix A). These models cover almost the entire spectrum of risk estimates that could be generated from existing mathematical extrapolation models. Generally statistical in character, these models are not derived from biological arguments, except for the multistage model, which has been used to support the somatic mutation hypothesis of carcinogenesis (Armitage and Doll 1954, Whittemore 1978, Whittemore and Keller 1978). The main difference among these models is the rate at which the response function P(d) approaches zero or P(0) as dose d decreases. For instance, the probit model would usually predict a smaller risk at low doses than the multistage model because of the difference of the decreasing rate in the low-dose region. However, it should be noted that one could always artificially give the multistage model the same (or even greater) rate of decrease as the probit model by making some dose transformation and/or by assuming that some of the parameters in the multistage model are zero. This, of course, is not reasonable without knowing, a priori, what the carcinogenic process for the agent is. Although the multistage model appears to be the most reasonable or at least the most general model to use, the point estimate generated from this model is of limited value because it does not help to determine the shape of the dose-response curve beyond experimental exposure levels. Furthermore, point estimates at low doses extrapolated beyond experimental doses could be extremely unstable and could differ drastically, depending on the amount of the lowest experimental dose. Since upper-bound estimates from the multistage model at low doses are relatively more stable than point estimates, it is suggested that the upper-bound estimate for the risk (or the lower-bound estimate for the dose) be used in evaluating the carcinogenic potency of a suspect carcinogen. The upper-bound estimate can be taken as a plausible estimate if the true dose-response curve is actually linear at low doses. The upper-bound estimate means that the risks are not likely to be higher, but could be lower if the compound has a concave upward dose-response curve or a threshold at low doses. Another reason one can, at best, obtain an upper-bound estimate of the risk when animal data are used is that the estimated risk is a probability conditional to the assumption that an animal carcinogen is also a human carcinogen. Therefore, in reality, the actual risk could range from a value near zero to an upper-bound estimate.

9.3.2.4 Calculation of the Carcinogenic Potency of Tetrachloroethylene

9.3.2.4.1 Calculation on the Basis of Gavage Data. As indicated previously, data on hepatocellular carcinomas in female mice are analyzed by using either the data of time-to-event or the data of incidence rate.

The time-to-event data and the calculations of potency are presented in Appendix B. In this calculation, it is assumed that all animals that died and were found to have hepatocellular carcinomas died from these tumors. Strictly speaking, one knows only that the tumor occurred before the death of an animal, and that a tumor was observed. However, the carcinogenic potency estimates based on other assumptions do not differ greatly when the multistage model with a time factor t^k is used for low-dose extrapolation. This conclusion is generally true for life-threatening tumors, as observed by Krewski et al. (1983) using simulated data.

The data on hepatocellular carcinoma incidence rates are used to fit four different extrapolation models. The maximum likelihood estimates of the parameters in each of the four models are presented in Table A-1 in Appendix A. Table 9-5 presents the upper-bound and point estimates of the risk at 0.01, 0.05, 0.1, 0.5, and 1 mg/kg/day.

Both the probit and the Weibull models estimate much higher risk at these dose levels than the multistage and the one-hit models. The potency $q_1^* = 3.5 \times 10^{-2}$ mg/kg/day, calculated by the multistage model with a time factor, will be used for calculating the unit risk of tetrachloroethylene from drinking water. This potency is obtained when the dose in mg/surface area/day is assumed to be equally effective among species. If this assumption is made, then $q_1^* = 2.6 \times 10^{-3}$ mg/kg/day should be used for this calculation.

9.3.2.4.2 Calculation on the Basis of Human Epidemiologic Data. No sound epidemiologic data are available that could be used to estimate the carcinogenic potency of tetrachloroethylene. However, one study by Kaplan (1980) for NIOSH may be used to provide an estimation of the possible range of its potency. This is the retrospective cohort mortality study on dry-cleaning workers exposed to tetrachloroethylene. The author of this report concluded: "Based on the study results, cancer of the colon, which accounted for 11 observed deaths, appears to be the cause of death most likely to have resulted from occupational exposure in our cohort." For this reason, data on colon cancer have been selected by the CAG for the purpose of calculating the carcinogenic potency of tetrachloroethylene. In the present study, the standardized mortality ratio (SMR) for colon cancers is estimated to be 182, which is statistically significant at $P < 0.05$. There are no data on the concentration of tetrachloroethylene to which the cohort workers were exposed. Based on an industrial hygiene study by NIOSH (Kaplan 1980), Campbell et al. (1980) estimated that the average annual tetrachloroethylene exposure in dry-cleaning plants that used the chemical ranged approximately from 1 ppm for "coin-op" workers to 7 ppm for machine operators. The annual average exposure was calculated under the assumption that a worker worked 40 hours a week for 50 weeks in a year.

As an approximation, 0.8 ppm and 6 ppm will be used as lower limits and upper limits of lifetime exposures by the cohort workers. If exposure were 0.8 ppm, the carcinogenic potency would be:

TABLE 9-5. UPPER-BOUND (POINT) ESTIMATES OF RISK AT VARIOUS DOSE LEVELS, BASED ON THE DATA OF HEPATOCELLULAR CARCINOMAS IN FEMALE MICE (NCI 1977a)

Assumption of human equivalent dose[a]	Models	Risk at Dose Levels (mg/kg/day)				
		0.01	0.05	0.1	0.5	1
Dose with surface corrections	Multistage with time factor	3.5×10^{-4} (1.8×10^{-4})	1.7×10^{-3} (8.8×10^{-4})	3.5×10^{-3} (1.8×10^{-3})	1.7×10^{-2} (8.8×10^{-3})	3.5×10^{-2} (1.8×10^{-2})
	Multistage	2.6×10^{-4} (2.0×10^{-3})	1.3×10^{-3} (1.0×10^{-3})	2.6×10^{-3} (2.0×10^{-3})	1.3×10^{-2} (1.0×10^{-2})	2.6×10^{-2} (2.0×10^{-2})
	Probit	1 (1.6×10^{-1})	1 (2.0×10^{-1})	1 (2.2×10^{-1})	1 (2.7×10^{-1})	1 (2.9×10^{-1})
	Weibull	1 (1.6×10^{-1})	1 (2.0×10^{-1})	1 (2.1×10^{-1})	1 (2.5×10^{-1})	1 (2.7×10^{-1})
	One-hit	2.6×10^{-4} (2.0×10^{-3})	1.3×10^{-3} (1.0×10^{-3})	2.6×10^{-3} (2.0×10^{-3})	1.3×10^{-2} (1.0×10^{-2})	2.6×10^{-2} (2.0×10^{-2})
Dose without surface correction	Multistage with time factor	2.6×10^{-5} (1.3×10^{-5})	1.3×10^{-4} (6.6×10^{-5})	2.6×10^{-4} (1.3×10^{-4})	1.3×10^{-3} (6.6×10^{-4})	2.6×10^{-3} (1.3×10^{-3})
	Multistage	2.0×10^{-5} (1.5×10^{-5})	1.0×10^{-4} (7.5×10^{-5})	2.0×10^{-4} (1.5×10^{-3})	1.0×10^{-3} (7.5×10^{-4})	2.0×10^{-3} (1.5×10^{-3})
	Probit	1 (1.1×10^{-1})	1 (1.4×10^{-1})	1 (1.5×10^{-1})	1 (1.9×10^{-1})	1 (2.1×10^{-1})
	Weibull	1 (1.4×10^{-1})	1 (1.6×10^{-1})	1 (1.8×10^{-1})	1 (2.1×10^{-1})	1 (2.3×10^{-1})
	One-hit	2.0×10^{-5} (1.5×10^{-5})	1.0×10^{-4} (7.5×10^{-5})	2.0×10^{-4} (1.5×10^{-4})	1.0×10^{-3} (7.5×10^{-4})	2.0×10^{-3} (1.5×10^{-3})

[a] Doses with surface correction assume that doses in mg/surface area/day are equally potent in producing cancer in humans and animals. Doses without surface correction assume that doses in mg/kg/day are equivalent between humans and animals.

$$B_1 = \frac{(1.82 - 1) \times 1.6 \times 10^{-2}}{0.8} = 1.6 \times 10^{-2}/\text{ppm}.$$

If exposure were 6 ppm, the carcinogenic potency would be:

$$B_2 = \frac{(1.82 - 1) \times 1.6 \times 10^{-2}}{6} = 2.2 \times 10^{-3}/\text{ppm}.$$

These estimates will be used to evaluate the reasonableness of the tetrachloroethylene potency estimations calculated on the basis of animal data.

9.3.2.5 Pharmacokinetic Data Relevant to Quantitative Risk Assessment--Although a large amount of pharmacokinetic data is available on experimental animals, the uses of these data for risk extrapolation are very limited because of the lack of corresponding human data. Based on the information in Table 9-7, taken from Pegg et al. (1979) and Schumann et al. (1980), it is suggested that the rate of tetrachloroethylene metabolism for mice is much higher than that for rats when animals are exposed via inhalation. However, the comparative metabolic rates of mice and rats do not appear to be different when the animals are exposed via gavage. The percentage of tetrachloroethylene that was expired unchanged from rats is consistent with that which was observed in humans when tetrachloroethylene was given by the inhalation route. No information is available on the human absorption rate of tetrachloroethylene via the oral route. For the oral route, if it is assumed that humans and rats are similar with respect to absorption rate, then the absorption rate for mice would be also similar to that of humans, because, on the basis of available information, mice and rats have a similar rate of absorption by this route of exposure.

TABLE 9-6. EXPIRED TETRACHLOROETHYLENE UNCHANGED AS PERCENTAGE OF RECOVERED RADIOACTIVITY
(Pegg et al. 1979, Schumann et al. 1980)

	Oral		Inhalation	
	1 mg/kg	500 mg/kg	10 ppm	600 ppm
Rats	72%	90%	68%	88%
Mice	NA	83%	12%	NA

NA = Not available.

9.3.2.6 Risk Associated With 1 ug/liter of Tetrachloroethylene in Drinking Water--As discussed above, it is reasonable to assume that both humans and mice have similar absorption rates for tetrachloroethylene. Therefore, the carcinogenic potency $q_1^* = 3.5 \times 10^{-2}/(\text{mg/kg/day})$, estimated from the mice gavage data, is used herein to calculate the unit risk of tetrachloroethylene in drinking water. Under the assumption that daily water consumption for a 70-kg person is 2 liters, the risk from drinking water containing 1 ug/liter of tetrachloroethylene is estimated as follows: $P = 3.5 \times 10^{-2}/(\text{mg/kg/day}) \times 10^{-3}\ (\text{mg/ug}) \times 2\ (\text{liter/day}) \div 70\ \text{kg} = 1 \times 10^{-6}$.

9.3.2.7 Risk Associated With 1 ug/m^3 of Tetrachloroethylene in Air--The carcinogenic potency $q^* = 3.5 \times 10^{-2}/(\text{mg/kg/day})$ estimated from the data in the NCI mice gavage study (1977a) is used herein to calculate the carcinogenic risk from tetrachloroethylene by inhalation. The relative absorption rate of tetrachlorothylene by inhalation and by gavage is not known. As an approximation, it is assumed that the effective dose by inhalation in mice is one-sixth of that by gavage. This assumption is based on the pharmacokinetic data presented in Table 9-7 and on the observation that absorption rates for tetrachloroethylene by the oral route are similar between mice and rats, since humans are assumed to be similar to rats with respect to absorption rate. To calculate the potency of tetrachloroethylene in terms of ug/m^3, it is assumed that the daily air intake for a 70-kg person is 20 m^3. Thus, for 1 ug/m^3 of tetrachloroethylene in air, the corresponding dose in mg/kg/day is

$$(1/6) \times (1\ \text{ug/m}^3) \times (20\ \text{m}^3/\text{day}) \times (1/70\ \text{kg}) \times (10^{-3}\ \text{mg/ug}) = 4.76 \times 10^{-5}\ \text{mg/kg/day}.$$

The carcinogenic potency of tetrachloroethylene by inhalation is calculated as follows:

$$q_1^* = (3.5 \times 10^{-2}) \times (4.76 \times 10^{-5}) = 1.7 \times 10^{-6}/(\text{ug/m}^3).$$

The risk associated with 1 ug/m^3 of tetrachloroethylene in air is thus estimated as 1.7×10^{-6}. Since 1 ppm of tetrachloroethylene is equivalent to 6,908 ug/m^3, the potency q_1^* in terms of ppm is estimated as

$$q_1^* = 1.7 \times 10^{-6} \times 6{,}908 = 1.0 \times 10^{-2}/\text{ppm}.$$

This estimate does not appear to be inconsistent with the crude estimates that have been calculated on the basis of human data. These range from 2.2×10^{-3}/ppm to 1.6×10^{-2}/ppm.

9.3.3 Comparison of Potency With Other Compounds

One of the uses of quantitative potency estimates is to compare the relative potencies of carcinogens. Figure 9-5 is a histogram representing the frequency distribution of potency indices for 53 suspect carcinogens evaluated by the CAG. The actual data summarized by the histogram are presented in Table 9-7. The potency index is derived from q_1^*, the 95% upper bound of the linear component in the multistage model, and is expressed in terms of $(\text{mMol/kg/day})^{-1}$. Where no human data were available, animal oral studies were used in preference to animal inhalation studies, since oral studies have constituted the majority of animal studies.

Based on available data concerning hepatocellular carcinomas in female mice, the potency index for tetrachloroethylene has been calculated as 6×10^0. This figure is derived by multiplying the slope $q_1^* = 3.5 \times 10^{-2}/(\text{mg/kg/day})$ and the molecular weight of tetrachloroethylene, 165.8. This places the potency index for tetrachloroethylene in the fourth quartile of the 53 suspect carcinogens evaluated by the CAG.

The ranking of relative potency indices is subject to the uncertainties involved in comparing a number of potency estimates for different chemicals based on varying routes of exposure in different species, by means of data from studies whose quality varies widely. All of the indices presented are based on estimates of low-dose risk, using linear extrapolation from the observational range. These indices may not be appropriate for the comparison of potencies if linearity does not exist at the low-dose range, or if comparison is to be made at the high-dose range. If the latter is the case, then an index other than the one calculated above may be more appropriate.

9.4 SUMMARY AND CONCLUSIONS

9.4.1 Qualitative

Tetrachloroethylene induced a statistically significant increase in the incidence of hepatocellular carcinomas in both high- and low-dose male and female B6C3F1 mice when administered by gavage for a period of 78 weeks. The tetrachloroethylene used was over 99% pure, but was estimated to contain epichlorohydrin

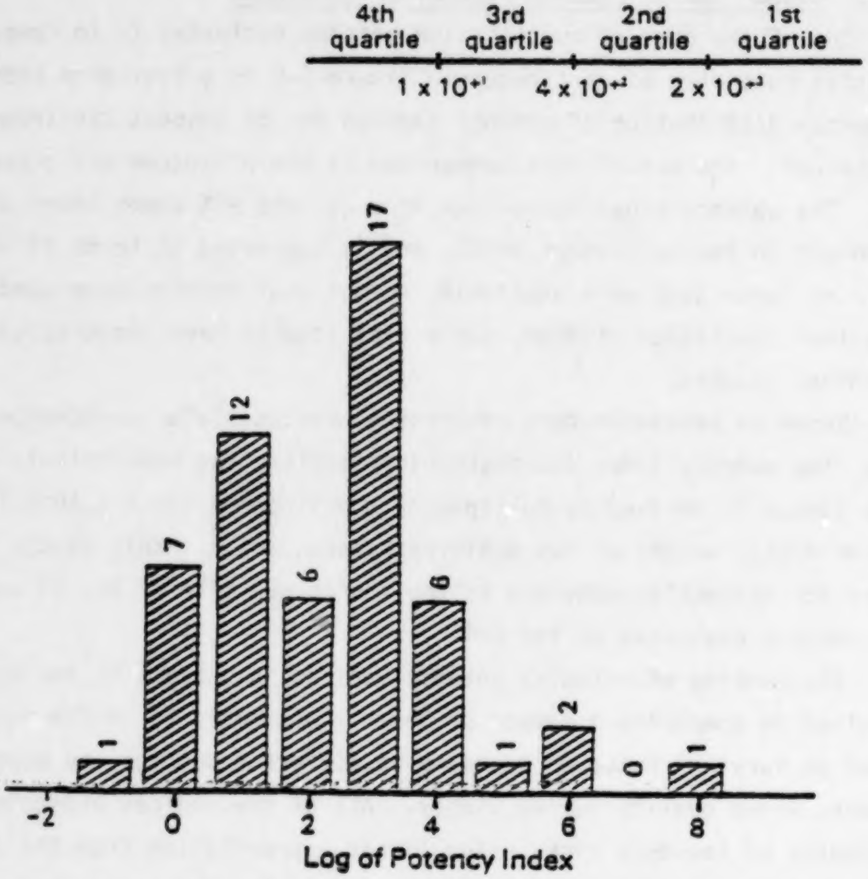

Figure 9-5. Histogram representing the frequency distribution of the potency indices of 53 suspect carcinogens evaluated by the Carcinogen Assessment Group.

TABLE 9-7. RELATIVE CARCINOGENIC POTENCIES AMONG 53 CHEMICALS EVALUATED BY THE CARCINOGEN ASSESSMENT GROUP AS SUSPECT HUMAN CARCINOGENS[1,2,3]

Compounds	Slope (mg/kg/day)$^{-1}$	Molecular weight	Potency index	Order of magnitude (log$_{10}$ index)
Acrylonitrile	0.24(W)	53.1	$1x10^{+1}$	+1
Aflatoxin B_1	2924	312.3	$9x10^{+5}$	+6
Aldrin	11.4	369.4	$4x10^{+3}$	+4
Allyl Chloride	$1.19x10^{-2}$	76.5	$9x10^{-1}$	0
Arsenic	15(H)	149.8	$2x10^{+3}$	+3
B[a]P	11.5	252.3	$3x10^{+3}$	+3
Benzene	$5.2x10^{-2}$(W)	78	$4x10^{0}$	+1
Benzidene	234(W)	184.2	$4x10^{+4}$	+5
Beryllium	4.86	9	$4x10^{+1}$	+2
Cadmium	6.65(W)	112.4	$7x10^{+2}$	+3
Carbon tetrachloride	$1.30x10^{-1}$	153.8	$2x10^{+1}$	+1
Chlordane	1.61	409.8	$7x10^{+2}$	+3
Chlorinated ethanes				
1,2-dichloroethane	$6.9x10^{-2}$	98.9	$7x10^{0}$	+1
hexachloroethane	$1.42x10^{-2}$	236.7	$3x10^{0}$	0
1,1,2,2-tetrachloroethane	0.20	167.9	$3x10^{+1}$	+1
1,1,1-trichloroethane	$1.6x10^{-3}$	133.4	$2x10^{-1}$	-1
1,1,2-trichloroethane	$5.73x10^{-2}$	133.4	$8x10^{0}$	+1
Chloroform	$7x10^{-2}$	119.4	$8x10^{0}$	+1
Chromium	41	104	$4x10^{+3}$	+4
DDT	8.42	354.5	$3x10^{+3}$	+3
Dichlorobenzidine	1.69	253.1	$4x10^{+2}$	+3
1,1-dichloroethylene	$1.47x10^{-1}$(I)	97	$1x10^{+1}$	+1
Dieldrin	30.4	380.9	$1x10^{+4}$	+4

TABLE 9-7. (continued)

Compounds	Slope (mg/kg/day)$^{-1}$	Molecular weight	Potency index	Order of magnitude (log$_{10}$ index)
Dinitrotoluene	0.31	182	6x10^{+1}	+2
Diphenylhydrazine	0.77	180	1x10^{+2}	+2
Epichlorohydrin	9.9x10^{-3}	92.5	9x10^{-1}	0
Bis(2-chloroethyl)ether	1.14	143	2x10^{+2}	+2
Bis(chloromethyl)ether	9300(I)	115	1x10^{+6}	+6
Ethylene dibromide (EDB)	8.51	187.9	2x10^{+3}	+3
Ethylene oxide	0.63(I)	44.0	3x10^{+1}	+1
Heptachlor	3.37	373.3	1x10^{+3}	+3
Hexachlorobenzene	1.67	284.4	5x10^{+2}	+3
Hexachlorobutadiene	7.75x10^{-2}	261	2x10^{+1}	+1
Hexachlorocyclohexane				
technical grade	4.75	290.9	1x10^{+3}	+3
alpha isomer	11.12	290.9	3x10^{+3}	+3
beta isomer	1.84	290.9	5x10^{+2}	+3
gamma isomer	1.33	290.9	4x10^{+2}	+3
Methylene chloride	6.3x10^{-4}	84.9	5x10^{-2}	-1
Nickel	1.15(W)	58.7	7x10^{+1}	+2
Nitrosamines				
Dimethylnitrosamine	25.9(not by q$_1^*$)	74.1	2x10^{+3}	+3
Diethylnitrosamine	43.5(not by q$_1^*$)	102.1	4x10^{+3}	+4
Dibutylnitrosamine	5.43	158.2	9x10^{+2}	+3
N-nitrosopyrrolidine	2.13	100.2	2x10^{+2}	+2
N-nitroso-N-ethylurea	32.9	117.1	4x10^{+3}	+4
N-nitroso-N-methylurea	302.6	103.1	3x10^{+4}	+4
N-nitroso-diphenylamine	4.92x10^{-3}	198	1x10^{0}	0
PCBs	4.34	324	1x10^{+3}	+3

TABLE 9-7. (continued)

Compounds	Slope $(mg/kg/day)^{-1}$	Molecular weight	Potency index	Order of magnitude ($\log_{10}$ index)
Phenols				
2,4,6-trichlorophenol	1.99×10^{-2}	197.4	4×10^{0}	+1
Tetrachlorodioxin	4.25×10^{5}	322	$1\times10^{+8}$	+8
Tetrachloroethylene	3.5×10^{-2}	165.8	6×10^{0}	+1
Toxaphene	1.13	414	$5\times10^{+2}$	+3
Trichloroethylene	1.9×10^{-2}	131.4	2.5×10^{0}	0
Vinyl chloride	1.75×10^{-2}(I)	62.5	1×10^{0}	0

Remarks:

1. Animal slopes are 95% upper-limit slopes based on the linearized multistage model. They are calculated based on animal oral studies, except for those indicated by I (animal inhalation), W (human occupational exposure), and H (human drinking water exposure). Human slopes are point estimates based on the linear non-threshold model.

2. The potency index is a rounded-off slope in $(mMol/kg/day)^{-1}$ and is calculated by multiplying the slopes in $(mg/kg/day)^{-1}$ by molecular weight of the compound.

3. Not all of the carcinogenic potencies presented in this table represent the same degree of certainty. All are subject to change as new evidence becomes available.

concentrations of less than 500 ppm. It is unlikely that this response could be attributed to the low concentration of epichlorohydrin.

No carcinogenic effect was observed in lifetime studies of Osborne-Mendel rats given tetrachloroethylene by gavage or in Sprague-Dawley rats exposed via inhalation for 12 months followed by 12 months of observation. However, because of excessive dose-related mortality in the gavage experiment, and because of the low dose level in the inhalation study, no conclusions can be made about the carcinogenicity of tetrachloroethylene in rats. A gavage study in four rat strains, now in progress at the National Toxicology Program (NTP), should clarify the nature of the rat response.

Intraperitoneal injection of tetrachloroethylene in strain A mice induced no statistically significant incidence of pulmonary adenomas. In mouse skin initiation experiments, tetrachloroethylene did not initiate skin tumors, nor did it induce skin tumors when applied alone three times per week for the lifetime of the animals. However, because of inherent limitations in these assays, the negative results they showed do not detract from the positive findings of the National Cancer Institute (NCI) mouse experiment.

In a cohort study of dry-cleaning workers exposed to tetrachloroethylene, it was found that these workers were at an elevated risk of colon cancer mortality; however, it was also the case that as many as one half of these workers may have been exposed to petroleum distillates earlier in their working history. Other studies either completed or currently in progress of dry-cleaners or of cancer cases for which employment in the dry-cleaning occupation was found to be a risk factor did not attempt to identify workers by tetrachloroethylene exposure.

9.4.2 Quantitative

Data on hepatocellular carcinomas in female mice from the NCI (1977a) gavage study on tetrachloroethylene have been used herein to calculate the risk associated with drinking water contaminated with tetrachloroethylene. Although the available pharmacokinetic data suggest that humans absorb less tetrachloroethylene than mice via inhalation exposure, the same conclusion cannot be made concerning exposure via the oral route.

Under the assumption that absorption rates for humans and mice are similar, the upper-bound cancer risk due to drinking water containing 1 ug/liter of tetrachloroethylene is estimated to be 1×10^{-6}.

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for Tetrachloroethylene (Perchloroethylene)

The upper-bound cancer risk associated with 1 ug/m^3 of tetrachloroethylene in air is estimated to be 2×10^{-6}. This is calculated on the basis of data obtained from the NCI gavage study in mice (1977a), under the assumption that the effective dose by inhalation in mice is one-sixth of that by gavage, and the consequent assumption that tetrachloroethylene in air is about six times more potent in mice than in humans.

The resultant estimate of the carcinogenic potency of tetrachloroethylene in air is 1.0×10^{-2}/ppm. This does not appear to be inconsistent with the potency estimate based on the NIOSH epidemiologic study (Kaplan 1980), which is a crude risk estimate ranging from 2.2×10^{-3}/ppm to 1.6×10^{-2}/ppm.

9.4.3 Conclusions

Tetrachloroethylene has been demonstrated to induce malignant tumors of the liver in both male and female mice of the B6C3F1 strain. This constitutes limited evidence that tetrachloroethylene may be carcinogenic in humans. It should be recognized that there is a substantial body of opinion in the scientific community to the effect that the mouse liver overreacts to chlorinated organic compounds in contrast to that of the rat, and that the induction of liver cancer in the mouse represents only a promoting action for spontaneous liver tumors which normally occur with substantial incidence.

According to the criteria of the International Agency for Research on Cancer (IARC), the data supporting the carcinogenicity of tetrachloroethylene must be classified as "limited." Since existing human epidemiologic data for tetrachloroethylene is inconclusive, its overall IARC ranking should be Group 3, meaning that there is inadequate evidence for classifying tetrachloroethylene as a human carcinogen.

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APPENDIX A

COMPARISON AMONG DIFFERENT EXTRAPOLATION MODELS

Four models used for low-dose extrapolation, assuming the independent background, are:

Multistage: $P(d) = 1 - \exp[-(q_1 d + \ldots + q_k d^k)]$

where q_i are non-negative parameters.

Probit: $$P(d) = \int_{-\infty}^{A + B\ln(d)} f(x)\,dx$$

where f(.) is the standard normal probability density function

Weibull: $P(d) = 1 - \exp[-bd^k]$

where b and k are non-negative parameters

One-hit: $P(d) = 1 - \exp[-bd]$

where b is a non-negative parameter.

The maximum likelihood estimates (MLE) of the parameters in the multistage and one-hit models are calculated by means of the program GLOBAL82, which was developed by Howe and Crump (1982). The MLE estimates of the parameters in the probit and Weibull models are calculated by means of the program RISK81, which was developed by Kovar and Krewski (1981).

Table A-1 presents the MLE of parameters in each of the four models.

TABLE A-1. MAXIMUM LIKELIHOOD ESTIMATE OF THE PARAMETERS FOR EACH OF THE FOUR EXTRAPOLATION MODELS BASED ON HEPATOCELLULAR CARCINOMAS IN FEMALE MICE (doses in mg/kg/day)

Basis of interspecies extrapolation	Multistage	Probit	Weibull	One-hit
Body surface area	$q_1 = 2.00 \times 10^{-2}$ $q_2 = 0$	$A = - 0.55$ $B = 9.80 \times 10^{-2}$	$b = 0.33$ $k = 0.12$	$b = 2.00 \times 10^{-2}$
Body weights	$q_1 = 1.5 \times 10^{-3}$ $q_2 = 0$	$A = -0.80$ $B = 9.80 \times 10^{-2}$	$b = 0.25$ $k = 0.12$	$b = 1.51 \times 10^{-3}$

APPENDIX B

TIME-TO-EVENT DATA AND CALCULATIONS OF POTENCY

TABLE B-1. TIME-TO-DEATH IN WEEKS (H INDICATES THAT AN ANIMAL DIED OR WAS SACRIFICED AND WAS FOUND TO HAVE A HEPATOCELLULAR CARCINOMA. ALL ANIMALS WERE SACRIFICED AT 91 WEEKS).

Control group (vehicle): 20 animals

90, 90, 90, 90, 90, 90, 90, 90, 90, 90, 90, 90, 90, 90, 90, 90, 90, 90
90, 90, 90, 90, 90, 90, 69, 90, 90, 90, 90, 90, 90, 90, 90, 90, 90, 90
90, 90, 90, 90, 90, 90, 90, 90, 90, 90, 90, 90, 90, 90, 68.

Low-dose group: 50 animals

91(H), 62, 61(H), 61, 60, 59
58, 57, 47, 23, 91(H), 83
66, 66, 66(H), 64, 62, 62
57, 50(H), 91(H), 91(H), 68, 67
65(H), 63, 62, 62, 55, 21
91(H), 91(H), 91(H), 91(H), 52,
50, 50, 48, 48, 41(H), 91(H)
91(H), 91(H), 87(H), 52, 51, 51(H)
49(H), 45, 44

High-dose group: 50 animals

91(H), 91(H), 91(H), 63, 53, 50, 50(H)
49, 46, 46, 91(H), 91(H), 72(H), 50
50(H), 49, 46, 45, 23, 22, 91(H)
87(H), 56, 55(H), 55(H), 52, 50, 50
50, 49, 46, 91, 58(H), 56, 56(H)
56, 56, 54(H), 50(H), 49, 49,
56(H), 53, 53, 52(H), 50(H), 49,
48, 24, 26, 17

The dose-response function at a time t is assumed to have the form

$$P(d/t) = 1 - \exp\left[-q(d) \times f(t)\right]$$

where

$$q(d) = q_0 + q_1 d + q_2 d^2$$

and

$$f(t) = t^k.$$

The lifetime cancer risk is calculated when t is set equal to 90 weeks. When the dose unit is mg/kg/day, the maximum likelihood estimates of the parameters are $q_0 = 0$, $q_1 = 1.6 \times 10^{-9}$, $q_2 = 2.3 \times 10^{-11}$, and $k = 3.6$. At $t = 90$ weeks, the 95% upper-bound estimate of the linear component of the dose-response model is $q_1^* = 3.5 \times 10^{-2}$ mg/kg/day. These estimates are calculated using the computer program WEIBULL82, developed by Howe and Crump (1982). In the calculation, only the tumors that were observed before week 91 are considered to be the causes of death for those animals in which the tumors were observed.